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Lisa Rachel Staimez Date

The Pathophysiology of Diabetes and Prediabetes:
Understanding the Relative Roles of Impaired Beta-Cell Function
and Insulin Resistance in Asian Indians
By

Lisa Rachel Staimez

Doctor of Philosophy

Graduate Division of Biological and Biomedical Sciences

Nutrition and Health Sciences

_____

K. M. Venkat Narayan, M.D.

Advisor

_____ _____

Edward Gregg, Ph.D. Ngoc-Anh Le, Ph.D.

Committee Member Committee Member

_____ _____

Qi Long, Ph.D. Lawrence S. Phillips, M.D.

Committee Member Committee Member

Accepted:

_____

Lisa A. Tedesco, Ph.D.

Dean of the James T. Laney School of Graduate Studies

_____

Date

The Pathophysiology of Diabetes and Prediabetes: Understanding the Relative Roles of Impaired Beta-Cell Function and Insulin Resistance in Asian Indians

By

Lisa Rachel Staimez

B.S., University of Arizona, 1999

M.P.H., Yale University, 2003

Advisor: K.M. Venkat Narayan, M.D., M.Sc., M.B.A.

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Abstract

The Pathophysiology of Diabetes and Prediabetes:
Understanding the Relative Roles of Impaired Beta-Cell Function
and Insulin Resistance in Asian Indians

By Lisa Rachel Staimez

Type 2 diabetes is a wide-reaching, global disease, strongly linked to obesity, unhealthy nutrition, and physical inactivity. Both insulin resistance and beta-cell dysfunction are known causes of the disease, yet questions exist regarding the roles of these two factors in the pathophysiology of diabetes. Asian Indians, a high-risk population for diabetes, have phenotypic characteristics that appear related to poor beta-cell function as well as insulin resistance, and thus, Asian Indians may be an informative population in detangling pathophysiological questions surrounding these two factors. This study examined 1,285 individuals without known diabetes who were screened in the **D**iabetes **C**ommunity **L**ifestyle **I**mprovement **P**rogram in Chennai, India. Individuals had a 75g OGTT with glucose and insulin measured at 0, 30, and 120 min. Measures included insulin resistance (HOMA-IR), insulin sensitivity (1/fasting insulin), and beta-cell function (DI_o = [ΔI0-30 /ΔG0-30] x [1/fasting insulin]), and HbA1c (%). Cross sectional and longitudinal analyses consisted of polytomous logistic regression, multiple linear regression, and piecewise spline analysis. Major findings included: (1) decreases in beta-cell function were marked between normoglycemic (NGT) individuals and those with prediabetes; changes in the rate of decline for beta-cell function were detected at 5.0, 5.25, 6.25 mmol/L (90, 95, 113 mg/dL) for fasting glucose and 5.25, 5.75, and 7.5 mmol/L (95, 104, and 135 mg/dL) for two-hour postchallenge glucose; the tandem increases of insulin resistance were less dramatic between NGT and prediabetes, increasing steadily across the spectrum of glycemia; (2) beta-cell dysfunction is a critical factor for those with early dysglycemia (i.e., isolated impaired fasting glucose or isolated impaired glucose tolerance), above and beyond insulin resistance; and (3) among individuals with prediabetes at baseline, both beta-cell function and insulin resistance were significantly associated with glycemia at one year. Data from this large, community-based study of Asian Indians suggest that reduced beta-cell function is prominent at glycemic levels that are clinically defined as normoglycemia. Validation in representative, multi-ethnic cohorts is needed to corroborate these findings. Future lifestyle intervention studies should test the effects of improved diet, increased physical activity, and reduced body weight on both insulin resistance and beta-cell function for diabetes prevention and control.

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"Education is not the filling of a pail, but the lighting of fire."- W.B. Yeats.

The process of focused study for the last 5 years has been one that I value greatly. Concluding with more questions but also, thankfully, more ideas and tools for answers, I feel charged to move into a new phase of inquiry and investigate questions which will impact health across populations. I thank the Nutrition and Health Sciences program, Aryeh Stein, and Laura Kettel Kahn, for the opportunity to pursue advanced studies. I also thank the Molecules to Mankind Program for valuable insight in bridging the wide world of science for progress.

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Chapter 1: Introduction

Type 2 diabetes is a progressive, degenerative disease that affects more than 371 million people worldwide (1). As a wide-reaching, global disease, diabetes is strongly linked to obesity, unhealthy nutrition, and physical inactivity (2). While it is known that the two major pathophysiological factors of diabetes, insulin resistance and impaired beta-cell function, work jointly to create a state of hyperglycemia, models of disease development first suggested that insulin resistance precedes beta-cell dysfunction in a two-step process of conversion from normoglycemia to prediabetes (3) and from prediabetes to diabetes (4). Most recently, evidence of beta-cell dysfunction in the early stages of diabetes suggest that beta-cell function may have a more prominent and instigating role than previously realized (5). The purpose of this dissertation work is to examine the pathophysiology of diabetes, particularly beta-cell function and insulin resistance, in early stages of disease development. Given that diabetes is increasing in every country worldwide regardless of income level (6) and that diabetes is a major cause of long-term morbidities (7; 8), understanding the etiology of diabetes is an important medical and public health priority.

In **Chapter 2**, we present background on the prevalence and pathophysiology of diabetes, the nutritional risk factors most associated diabetes development, and how these risk factors impact Asians, an ethnic group that disproportionately experiences greater prevalence levels of diabetes (9). Prominent differences exist among ethnic groups in risk for diabetes and glucose intolerance (10), and varying rates of diabetes prevalence may be due to differences in levels of impaired beta-cell function and insulin resistance across populations. Asians, in particular, have been cited to experience high rates of

diabetes at younger ages and lower BMIs (9), and higher basal insulin levels (11), requiring Asian-specific cutoffs for obesity to better reflect risk of poor health outcomes (12). In **Chapter 3**, we present findings from a systematic review of overweight, obesity, and type 2 diabetes among specific Asian-American groups in the United States. Data were synthesized and summarized using available estimates on the prevalence of these conditions, and while comparisons were limited due to variability in study populations, methods, and definitions used in published reports, the results are suggestive of high prevalence of diabetes in Asian Indians regardless of weight status (13). The work presented in Chapter 3 was published in *Current Diabetes Reviews* in 2013.

Overarching methods used in this research are detailed in **Chapter 4**. We studied beta-cell function and insulin resistance in Asian Indian individuals without known diabetes who were screened in the **D**iabetes **C**ommunity **L**ifestyle **I**mprovement **P**rogram (D-CLIP) in Chennai, India (14). Participants were classified at baseline as having normoglycemia or prediabetes (2-hour blood glucose levels below 140 mg/dL and/or elevated fasting plasma glucose levels of 100 mg/dL or more). The D-CLIP trial offered a unique opportunity to investigate the impairment of beta-cell function earlier in the pathogenesis of diabetes by including those with impaired fasting glucose (IFG) defined at 100 mg/dL or greater. Other well-known lifestyle intervention trials, including the Diabetes Prevention Program (DPP), have generally recruited participants with impaired glucose tolerance (IGT) only (2-hour blood glucose at least 140 mg/dL) or with IFG defined with a minimum at 110 mg/dL for fasting plasma glucose.

Chapters 5-7 directly address the research aims of this dissertation. Please note that Chapter 5 has already been published, and Chapters 6 and 7 contain preliminary data

with plans for publication in peer-reviewed journals after submission of this dissertation. Below, we outline the specific research aims addressed in each chapter and hypotheses.

Research Aim 1 (Chapter 5)

Examine cross sectional, relative contributions of beta-cell function (i.e., oral disposition index, DI_o) and insulin resistance (i.e., HOMA-IR) to mild dysglycemia (i.e., isolated impaired fasting glucose, iIFG, and isolated impaired glucose tolerance, iIGT) in Asian Indians from Chennai, India.

The hypothesis for Aim 1 is that the magnitude of association between beta-cell function and mild dysglycemia will be greater than that of insulin resistance and mild dysglycemia. Findings for Aim 1 have been published in *Diabetes Care* 2013.

Research Aim 2 (Chapter 6)

Identify potential change points across glycemia (i.e., fasting plasma glucose, 2-hour post-challenge glucose load, and HbA1c) for significant changes in the rates of association between (a) glycemia and beta cell function (i.e., DI_o) and (b) glycemia and insulin resistance (i.e., HOMA-IR) among Asian Indians with normoglycemia or prediabetes.

The hypothesis for Aim 2 is that significant change points will be detected in the linear relationship of glycemia and estimated beta-cell function, even across normoglycemia. However, change points will not be detected in the relationship between glycemia and

estimated insulin resistance. Findings for Aim 2 are presented in Chapter 6 in a pre-submission manuscript format.

Research Aim 3 (Chapter 7)

Examine the relationship of baseline beta-cell function (i.e., DI_o) relative to baseline insulin resistance (i.e., HOMA-IR) across glycemia (i.e., fasting plasma glucose, 2-hour post-challenge glucose load, and HbA1c) at one-year follow up in Asian Indians.

The hypothesis for Aim 3 is that baseline beta-cell function is a significant predictor of glycemia at one-year, above and beyond baseline insulin-resistance. Findings for Aim 3 are presented in Chapter 7 in a pre-submission manuscript format.

Finally, in **Chapter 8**, overall research findings are discussed in the context of other recent research and in the context of the limitations and strengths of the entire study. Lastly, the overall implications of this research are considered, and suggestions for future research are provided.

Chapter 2: Background

Diabetes is a complex metabolic disorder that can often be asymptomatic, resulting in progressive, long-term implications that are costly. In fact, 50% of individuals with diabetes do not know that they have the disease (1). The irreversible development of complications, including neuropathy, retinopathy, and kidney disease, along with associated functional morbidities (e.g., physical and cognitive), requires management by health services (15), generating medical costs, opportunity costs (16), and premature mortality. On average, those with diabetes lose eight years from their lifespan compared to those without diabetes (17). An important area of research for diabetes surveillance and prevention includes research on the pathophysiology of disease and understanding how and why diabetes develops. In the following section, we provide general information regarding the prevalence of diabetes and prediabetes, the pathophysiological factors that lead to the diabetes, and nutrition-related risk factors. We also discuss these topics as related to Asian populations.

Prevalence of Diabetes and Prediabetes

Diabetes is defined as fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL) or 2-hour post-load glucose ≥ 11.1 mmol/L (200 mg/dL) or HbA1c ≥ 6.5% or random glucose ≥ 11.1 mmol/L in the presence of symptoms (i.e., and any combination of these) (8). The prevalence of diabetes ranges from 4.3% in Africa to 10.9% in the Middle East and North Africa, and 50% of all cases are undiagnosed (1). The rates of diabetes are expected to rise steadily, and in the U.S., 29.6 million people will have diabetes by 2030 (6). Over 40% of people aged ≥ 20 years have hyperglycemic conditions (i.e., diabetes or

prediabetes), and the prevalence is even higher in U.S. minorities. American Indians and Alaska Natives have the highest age-adjusted prevalence of diabetes among all U.S. racial and ethnic groups at 16.3% (18). In 2005-2006, age- and sex-standardized prevalence of diagnosed diabetes was approximately twice as high in non-Hispanic blacks ($P < 0.0001$) and Mexican Americans ($P = 0.0001$) compared with non-Hispanic whites, although undiagnosed diabetes was not higher (19). Furthermore, U.S. national data suggest that Asians, particularly Asian Indians may have markedly high rates of diabetes (20). **Chapter 3** provides a systematic review of the prevalence of diabetes among Asian subgroups in the United States. Outside of the U.S., almost one fifth of all people with diabetes worldwide are from the Southeast Asia region (71.4 million adults) (6). Furthermore, China, India, Bangladesh, Indonesia and Pakistan are expected to be listed among the top ten countries with the greatest number of people affected by diabetes by 2030 (6). While these large numbers may be a reflection of large population sizes, they may also reflect factors resulting from rapid socioeconomic and nutrition transitions (e.g., increased population aging and gain in body mass index, BMI) along with, environmental and genetic influences (21).

Prediabetes, a high-risk state for the development of diabetes and related complications, is defined as impaired fasting glucose, IFG, which is fasting plasma glucose at 5.6-6.9 mmol/L (100-125 mg/dl); or impaired glucose tolerance, IGT, which occurs when 2-hr postchallenge glucose 7.8 - 11.0 mmol/L (140 - 199 mg/dL); or elevated HbA1c, when HbA1c 5.7–6.4% (8). Worldwide, it is estimated that the prevalence of IGT is 7.9% (344 million adults), and global predictions suggest that 470 million people will have prediabetes by 2030 (6). If 70% of individuals with prediabetes

eventually progress to diabetes (22), then an improved understanding of how to prevent both prediabetes and diabetes is greatly needed.

Among U.S. adults aged ≥ 18 years, the prevalence of prediabetes (i.e., using fasting plasma glucose or HbA1c) increased from 29.2% (26.8–31.8) to 36.2% (34.5–38.0) from 1999-2010 (23). Large populations with IFG and/or IGT are found in Asia as well, representing a large pool of people that are at high risk of developing diabetes and associated complications (2). Among 24,335 subjects from 11 Asian countries and 4 studies with participants aged 30-89 years, Indian subjects had a higher prevalence of impaired glucose regulation (IFG or IGT) in the younger age-groups (30-49 years) compared with that for Chinese and Japanese subjects (24). The repercussions of high prediabetes prevalence is exemplified in the Indian Diabetes Prevention Programme, where over half of the Asian Indian population with pre-diabetes developed diabetes during three years of follow up (25). The high rates of diabetes (diagnosed and undiagnosed) and prediabetes in Asia highlight the critical need for a more thorough understanding of disease processes to efficiently detect and prevent diabetes in the region and elsewhere worldwide.

Pathophysiology of Diabetes

Both insulin resistance and poor beta-cell function lead to elevated blood glucose and, in turn, diabetes. As increased rates of glucose are released by the liver and kidneys and glucose disposal is decreased, metabolic dysfunction is compounded by decreased clearance of glucose by the kidneys, deepening the state of hyperglycemia (26). In the

following section, we provide a brief introduction to insulin resistance and poor beta-cell function, with greater discussion presented in **Chapters 5, 6, 7,** and **8**.

Insulin Resistance

Insulin resistance is a result of poor insulin-stimulated glucose uptake in muscle, liver, and fat cells. Multiple post-receptor intracellular defects impair glucose transport, glucose phosphorylation, glucose oxidation, and glycogen synthesis (27). Specific defects may include reduced insulin receptor tyrosine phosphorylation, decreased IRS-1 tyrosine phosphorylation, decreased PI3-kinase activation, impaired GLUT transporter translocation, decreased glucose phosphorylation, and impaired glycogen synthase (27). A key mechanism behind insulin resistance is the accumulation of a lipid, diacylglycerol, within key tissues, thereby activating other proteins (e.g., protein kinase C enzymes) and leading to the production of tissue-specific forms of novel protein kinase C molecules (nPKC), which ultimately interfere with insulin signaling (28). These processes lead to insulin resistance and places individuals at greater risk of prediabetes and diabetes.

Ethnicity influences one's susceptibility to diabetes (29), and Asian populations tend to experience a high prevalence of insulin resistance (30). Asians may be vulnerable to insulin resistance due to a high ratio of fat mass to low lean mass, harboring a high ratio of visceral adiposity in particular (31; 32). They have low thresholds for factors associated with insulin resistance, including age and BMI (30), and thus, Asians tend to develop diabetes at younger ages and lower BMIs compared to some other ethnicities like whites. South Asians, in particular, may have high levels of insulin resistance compared to other Asian and non-Asian groups (33; 34), even after adjustment for age and BMI.

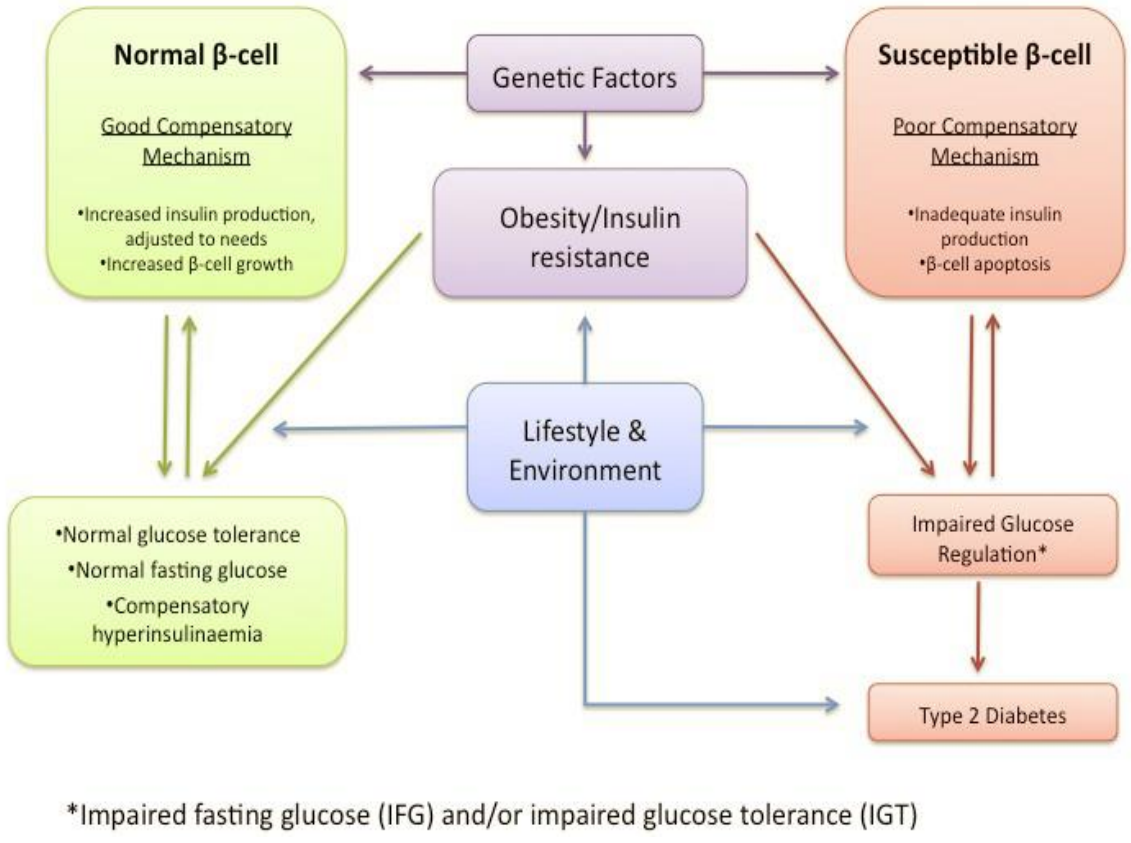
Poor Pancreatic Beta-Cell Function

Pancreatic beta-cells produce insulin which enables insulin-sensitive tissues (i.e., muscle, liver, adipose) to take up glucose. Beta-cell function refers to the ability of pancreatic beta-cells to produce insulin at sufficient levels for the body's needs; these levels vary according to the body's levels of insulin sensitivity (35). Beta-cells release insulin in two phases. The first phase represents exocytosis of insulin from secretory vesicles docked to the membrane of beta-cells. The second phase appears to result from the recruitment of secretory vesicles from a reserve pool, leading to additional insulin granule translocation and maturation (36; 37). During periods of low insulin sensitivity (i.e., high insulin resistance), beta-cells compensate by producing additional insulin. Thus, good beta-cell function implies that the beta-cells are able to cope with periods of increased insulin resistance (e.g., during obesity or pregnancy) and produce greater amounts of insulin, further maintaining metabolic homeostasis (2). For some individuals, beta-cell function eventually reaches a point where insulin secretion is insufficient. For example, when fasting hyperglycemia is present, beta-cell function has already decreased by about 75% (5). This reduction may reflect a loss of 1st phase or a loss of 1st and 2nd phase insulin secretion (36).

Some recent studies have suggested that Asian populations along with others may be susceptible to poor insulin secretion. These studies have detected low levels of insulin secretion in Chinese, Japanese Americans, Koreans with states of early dysglycemia (i.e., isolated IFG or isolated IGT) or normoglycemia (38-42). These results bring to question previously postulated mechanism of diabetes pathogenesis, in which impaired insulin sensitivity prompts compensatory increases in insulin secretion, and for some, an

eventual exhaustion of beta-cells and associated beta-cell dysfunction leading to subsequent insulin deficiency (43; 44). Contrary to this approach, recent work has suggested that *pre-existing* abnormalities surrounding beta-cell function may be present in some populations, also suggesting a possibility for *early* susceptibility to impaired beta-cell function (5). **Figure 2-1** below depicts how early susceptibility to impaired beta-cell function may lead to an endpoint of diabetes development. More evidence regarding the role of beta-cell dysfunction in the early pathogenesis of diabetes is needed to better inform diabetes prevention and treatment.

Figure 2-1. Early susceptibility to impaired beta-cell function and development of type 2 diabetes mellitus **(adapted from Kahn 2006 (5; 14))**

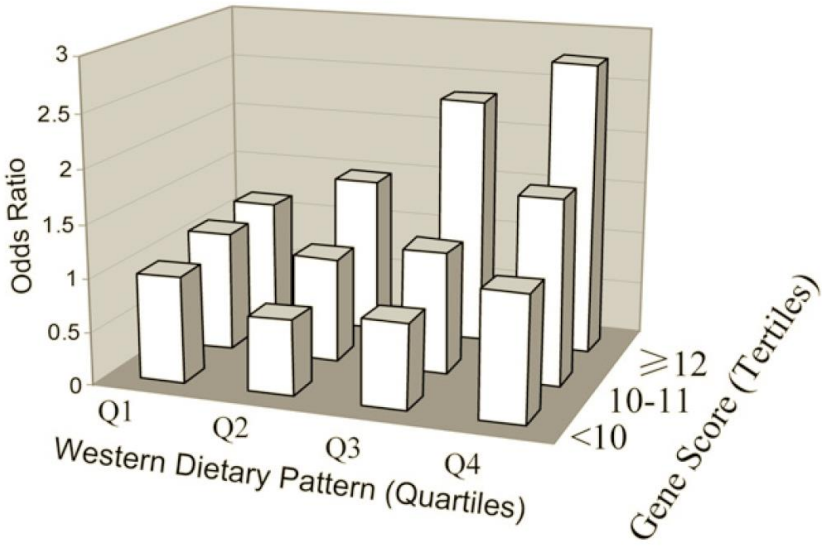


Nutrition-Related Risk Factors for Diabetes

Diet

The most common clinical approach for preventing hyperglycemia is recommending changes in lifestyle that incorporate a healthier diet and more physical activity. A common theme of healthier diets includes reducing the quantity of calories consumed. High quantities of consumed calories increase overweight (i.e., including obesity), and over time, an excessive caloric intake degrades metabolic homeostasis and hepatic glucose control. A second important theme includes modification of the quality of dietary components. Low quality diets consist of simple carbohydrates, saturated dietary fats, trans fats, and processed foods. Diets with high proportions of these low quality categories lead to increased diabetes risk through insulin resistance and, possibly, reduced beta-cell function (45-48), particularly among those with genetic predisposition to diabetes (49). As shown in Health Professionals Follow-Up Study (**Figure 2-2**), odds of diabetes risk were highest among those scoring highest on the Western Diet Pattern and having the highest genetic risk score for diabetes as compared to those in the lowest categories (49). In the early stages of diet-induced insulin resistance, a change in plasma free fatty acid concentrations may directly, through beta-cell signaling, or indirectly, by decreasing hepatic insulin clearance, result in compensatory insulin secretion (50). Several studies have examined foods or nutrients on beta-cell function (e.g., coffee, vitamin D), however mixed results have made these association unclear (51-53). More research is needed to examine the associations of diet on beta-cell function, independent of insulin resistance.

Figure 2-2. Synergy of diet and genetic susceptibility on diabetes risk among white men in the Health Professionals Follow-Up Study (n= 2,533) from Qi and colleagues (49). Odds ratios were calculated by using an unconditional logistic regression model. Western dietary pattern scores were presented in quartiles and genetic risk scores was presented in three categories (10, 10–11, and ≥12). Analyses were adjusted for age, BMI, smoking, alcohol consumption, physical activity, family history of diabetes, and total energy intakes.



Diet in Asian countries have changed as rates of diabetes have increased (54). Animal foods and fats now contribute a greater proportion of energy for individuals, along with other edible oils (e.g., vegetable ghee, which is high in trans-fats), sugars, polished rice, and refined wheat, all of which are more accessible and relatively cheaper than in the past due to global trade liberalization (45; 55). While Asian countries are experiencing varying levels of food security, food availability, cultural norms around

food (56), these changing dietary norms reflect different phases within the nutrition transition, where traditional diets are modified as demographic, economic, and epidemiological changes stimulate new patterns of food availability, quality, and quantity (57). Nevertheless, while diet, income, and food prices have undergone dramatic changes, knowledge, attitudes, and beliefs around nutrition and health have changed less dramatically, contributing to increased chronic diseases (58).

Physical activity

Along with diet, physical activity heavily impacts health and disease through its role in glucose metabolism, influencing glucose uptake from the blood and overall energy storage. Physical inactivity increases the risk of diabetes, with sedentary people exhibiting the highest risk (59). Exercise improves blood glucose levels by decreasing fatty acid metabolites and insulin resistance (28; 60) and improving glucose uptake by increasing the transport of glucose transporter type 4 to the plasma membrane (61; 62). The impact of exercise on beta-cell function is less understood. Preliminary evidence suggests that both moderate- and vigorous- intensity exercise training improves beta-cell function but possibly through distinct mechanisms (63), and more studies are needed to confirm these findings. Across Asia, as occupations have become less physically strenuous, individuals have experienced reduced levels of total physical activity (45), and the general trend towards a more sedentary lifestyle has contributed to the increased risk of chronic diseases. Lifestyle interventions in Asia that have increased physical activity levels have suggested a reduction in diabetes risk through reduced insulin resistance (64), but more studies are needed to test the independent and relative associations of increased exercise on beta-cell function.

Body Mass Index

BMI is a measure of overweight that is associated with a variety of metabolic conditions leading to insulin resistance. Induced through inflammation, oxidative stress, endoplasmic-reticulum stress, adipokines, and lipokines, insulin resistance can develop in the liver and in skeletal muscle which, over time, can lead to hyperglycemia and diabetes (28; 65; 66), particularly with an underlying genetic predisposition for diabetes (49). Ten years ago, a WHO expert consultation redefined BMI cut offs in Asians to better reflect r risk for cardiometabolic diseases (12). The expert panel recommended: BMI less than 18.5 kg/m^2 for underweight, 18.5–23 kg/m^2 for normal weight, 23–27.5 kg/m^2 for overweight, and 27.5 kg/m^2 or higher for obese. Nevertheless, even with these alternative definitions, the variation of diabetes in Asia and between Asia and other world regions cannot be fully explained by differences in BMI alone (2; 67; 68).

Abdominal Obesity

Abdominal obesity is a form of body fat distribution that influences glucose metabolism and diabetes, independent of BMI (67; 69; 70). Abdominal obesity reflects a surfeit in visceral adiposity, which increases insulin resistance, glucose intolerance, and the accumulation of damaging free fatty acids and inflammatory mediators (71-73). Racial differences in visceral adiposity have been studied (74; 75), and Asians, who appear leaner than those of alternative ethnic origin (i.e., as defined by BMI measurements), actually undergo greater allotment of excess calories to visceral fat (68). South Asians, in particular, have greater levels of total abdominal adipose tissue, subcutaneous abdominal adipose tissue, and visceral adipose tissue (55; 76). These findings suggest that Asians are at higher risk of diabetes, partly due to visceral adiposity.

Evidence from Lifestyle Interventions

Data from lifestyle intervention trials further support the important links between diet, physical activity, and diabetes prevention. Improved diet, increased exercise, and related weight loss are key lifestyle factors that counter hyperglycemia by improving insulin action and reducing hepatic glucose production (77). Among several major diabetes prevention trials worldwide, lifestyle programs that incorporated behavioral education with goals of improving diet, increasing exercise, and/or increasing weight loss successfully reduced diabetes risk in participants (2; 25; 77-79). These major trials recruited participants who were overweight and had IGT; the Diabetes Prevention Program (DPP), the Finnish Diabetes Prevention Study, the Indian Diabetes Prevention Program, and the Da Qing Study recruited participants with IGT who had 2-hour blood glucose levels of at least 140 mg/dL (25; 77-79). Thus, these patients were already near diabetes diagnosis, and as such, early susceptibility of diabetes has not been well studied. Furthermore, few lifestyle intervention trials have studied the effects of lifestyle interventions on beta-cell function. The DPP showed that lifestyle intervention is associated with preservation of beta-cell function (79). Two smaller studies showed contrary results of whether lifestyle interventions improve beta-cell function (80; 81), while a third study of very low calorie diet in obese with diabetes showed improvement in beta-cell function of morbidly obese (82). As such, more studies are needed to examine the effects of lifestyle interventions on beta-cell function by recruiting participants with a greater range of baseline blood glucose values, thereby including both people with low levels of abnormal fasting glucose as well as those with established IGT.

Chapter 3: A Systematic Review of Overweight, Obesity, and Type 2 Diabetes Among Asian American Subgroups

The following 19 pages:

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A Systematic Review of Overweight, Obesity, and Type 2 Diabetes Among Asian American Subgroups

Lisa R. Staimez[1,*], Mary Beth Weber[2], K.M. Venkat Narayan[1,2,3] and Reena Oza-Frank[2, 4]

[1]*Emory University, Laney Graduate School, Division of Biological and Biomedical Sciences, Nutrition and Health Sciences Program, Atlanta GA, USA*

[2]*Emory University, Rollins School of Public Health, Atlanta, GA, USA*

[3]*Emory University, School of Medicine, Atlanta, GA, USA*

[4]*Research Institute at Nationwide Children's Hospital and The Ohio State University, Columbus, OH, USA*

Abstract: This systematic review synthesizes data published between 1988 and 2009 on mean BMI and prevalence of overweight, obesity, and type 2 diabetes among Asian subgroups in the U.S. We conducted systematic searches in Pub-Med for peer-reviewed, English-language citations that reported mean BMI and percent overweight, obesity, and diabetes among South Asians/Asian Indians, Chinese, Filipinos, Koreans, and Vietnamese. We identified 647 database citations and 23 additional citations from hand-searching. After screening titles, abstracts, and full-text publications, 97 citations remained. None were published between 1988 and 1992, 28 between 1993 and 2003, and 69 between 2004 and 2009. Publications were identified for the following Asian subgroups: South Asian (n=8), Asian Indian (n=20), Chinese (n=44), Filipino (n=22), Korean (n= 8), and Vietnamese (n=3). The observed sample sizes ranged from 32 to 4245 subjects with mean ages from 24 to 78 years. Among samples of men and women, the lowest reported mean BMI was in South Asians (22.1 kg/m^2), and the highest was in Filipinos (26.8 kg/m^2). Estimates for overweight (12.8 - 46.7%) and obesity (2.1 – 59.0%) were variable. Among men and women, the highest rate of diabetes was reported in Asian Indians with BMI $\geq$ 30 kg/m^2 (32.9%, age and sex standardized). This review suggests heterogeneity among U.S. Asian populations in cardiometabolic risk factors, yet comparisons are limited due to variability in study populations, methods, and definitions used in published reports. Future efforts should adopt standardized methods to understand overweight, obesity and diabetes in this growing U.S. ethnic population.

Keywords: Asian, BMI, diabetes, ethnicity, obesity, overweight.

INTRODUCTION

Between 2000 and 2010, the United States (U.S.) Asian population grew by 46%, to 17.3 million, the highest percentage growth of any racial group during that time period. The three largest Asian American subgroups are Chinese (3.8 million), Filipino (3.2 million), and Asian Indian (2.8 million) [1]. Despite continued growth of general and specific Asian American sub-populations, studies still group them into one large category, potentially missing important heterogeneity in disease burden and risk. This is especially true with regard to overweight, obesity and diabetes, chronic conditions of increasing public health significance due to increasing prevalence worldwide. However, the estimated burden of these conditions across Asian American subgroups in the U.S. is difficult to quantify because data disaggregated by Asian American subgroups are fragmented in the literature. The aim of this review is to systematically synthesize data about overweight, obesity, and diabetes among specific Asian American groups. The resulting synthesis will qualitatively summarize available estimates on the prevalence of overweight, obesity, and diabetes among those specific Asian American subgroups with high immigration rates to the U.S. over the past 20 years, specifically South Asians (Asian Indian, Bangladeshi, Bhutanese, Pakistani, Nepalese, and Sri Lankan), Chinese, Filipino, Korean, and Vietnamese.

METHODS

We performed a systematic search for peer-reviewed studies published in English using PubMed (1988 – 2009). Search strategies included Medical Subject Heading (MeSH) terms and keywords. For overweight, obesity, and diabetes, search terms included "body mass index," "overweight," "obesity," "diabetes mellitus," and "diabetes mellitus, Type 2." The search terms for Asian groups included country ethnology, "emigrant," "immigrant," and "United States." Because South Asia and South Asian are both commonly used and capture some of the subgroups of interest, we decided to search for South Asia by keyword ("South Asian*"). Additional studies were retrieved through a hand search of the citations listed in the publications of PubMed search results and from recent review articles on the topics of interest.

*Address correspondence to this author at the 1518 Clifton Road, NE, CNR Rm. 7043, Atlanta, GA 30322, USA; Tel: (404) 712 – 1902; Fax: (404) 727 – 3350; E-mail: lisa.staimez@emory.edu

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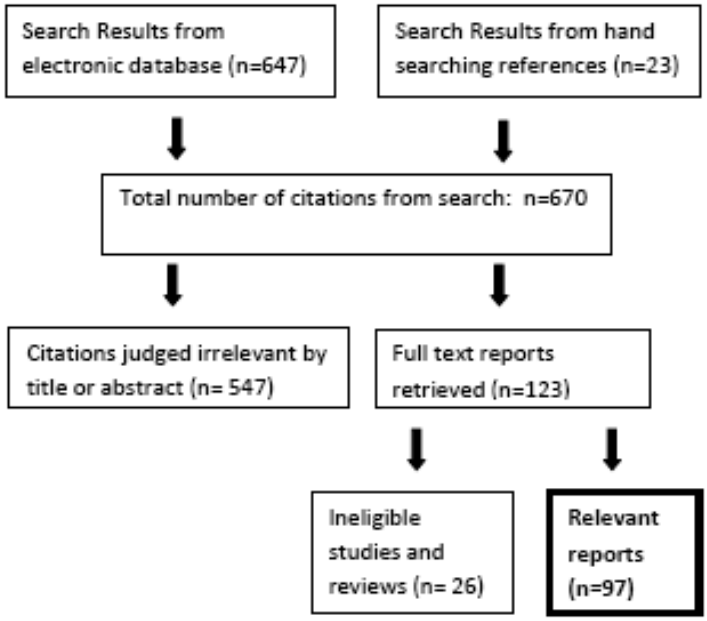


Legend 1. Studies were ineligible for the following reasons: BMI and percent overweight/obese and percent diabetes not provided (n=13); participant age (n= 6); study dates (n=2); sample size (n=1); review paper (n=1); other (n=3).

Fig. (1). Systematic review flow chart: report selection.

Inclusion And Exclusion Criteria

An article was eligible for inclusion if it presented original research in English language collected in the U.S. or a U.S. territory between 1988 and 2009, including 2009 electronic publications ahead of 2010 print. Inclusion criteria were designed to retrieve studies that reported prevalence of obesity, overweight, and diabetes among various Asian American subgroups (South Asians, Asian Indian, Pakistani, Bangladeshi, Sri Lankan, Chinese, Filipino, Korean, and Vietnamese). Articles containing study samples with origin from two or more South Asian countries were exclusively categorized into the South Asian subgroup. Given that Asian Indians, Pakistanis, etc. are part of South Asian ancestry, these categories could be combined for a more generalized analysis, however, for the purpose of this review, South Asian was treated as a separate category in accordance with database search strategies. Articles were included if they contained data on mean body mass index (BMI), percent overweight, percent obesity, or percent diabetes. Only articles with samples sizes of at least 30 participants in the specific Asian American subgroups of interest were included. Studies that included individuals less than 18 years of age, living outside the U.S., or participating in data collection outside the time period of interest (1988-2009) were excluded. Other exclusion criteria are listed as follows: studies that only selected for people with diabetes or other poor health conditions; studies using non-representative samples matched by BMI or diabetes; and studies examining gestational diabetes mellitus or weight change during pregnancy.

Study Selection

The selection of articles for inclusion was conducted through two screening phases. The first phase included a review of abstracts for inclusion and exclusion criteria. All abstracts were reviewed by the first reviewer (LRS) and by an independent second reviewer (MBW or ROF). Discrepancies about inclusion of studies were resolved through consensus with a third person serving as a non-reviewing arbitrator (MBW or ROF). Remaining abstracts were included in the second screening phase in which each reviewer applied inclusion and exclusion criteria to full-text articles.

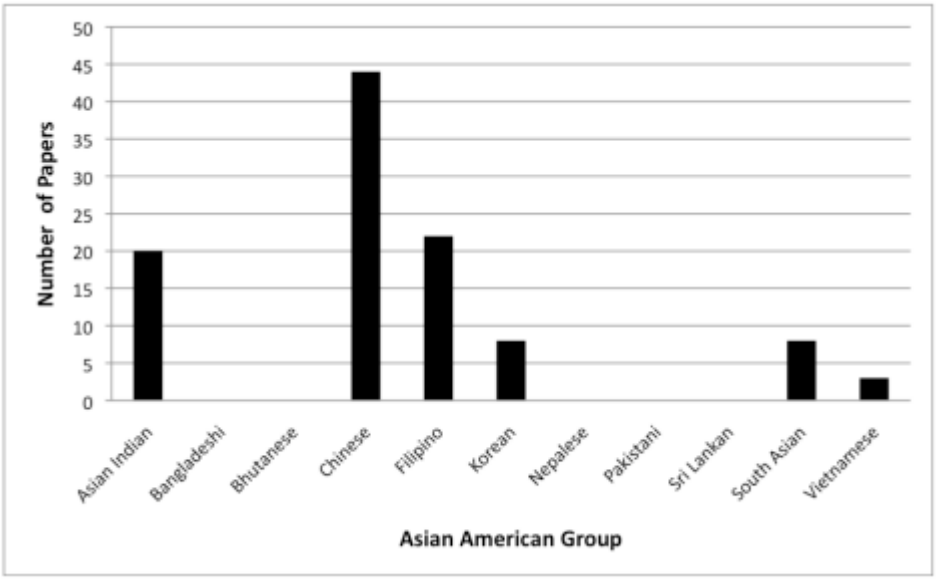
Data Extraction

For each publication retrieved and meeting inclusion and exclusion criteria, data were extracted using a standardized form. Key measures extracted included mean BMI, percent overweight or obese defined by BMI strata, and percent diabetes defined by self-report, fasting blood glucose, random (non-fasting) blood glucose, or two-hour, post challenge blood glucose. Percent overweight and percent obesity were defined as mutually exclusive ranges of BMI. Publications that defined overweight using a BMI range that lacked an upper BMI bound (e.g., BMI $\geq$25 kg/m^2) were included in this review, with data categorized into combined overweight and obesity. Other extracted data included study cohort, year(s) of data collection, study design, characteristics of the study population (ethnicity/nationality, sex, age range, etc.), sample size, and measurement methods (e.g., self-report, fasting blood glucose).

RESULTS

Literature Search

Our searches yielded 647 citations from PubMed and 23 citations from hand searching of references. After the first screening phase of titles and abstracts, 547 citations were excluded, leaving 123 articles for full-text review. The second screening phase of the full-text articles resulted in the exclusion of 26 additional articles, and 97 articles remained for data extraction (Fig. **1**). Disagreement between reviewers occurred for only nine citations (1.3%).



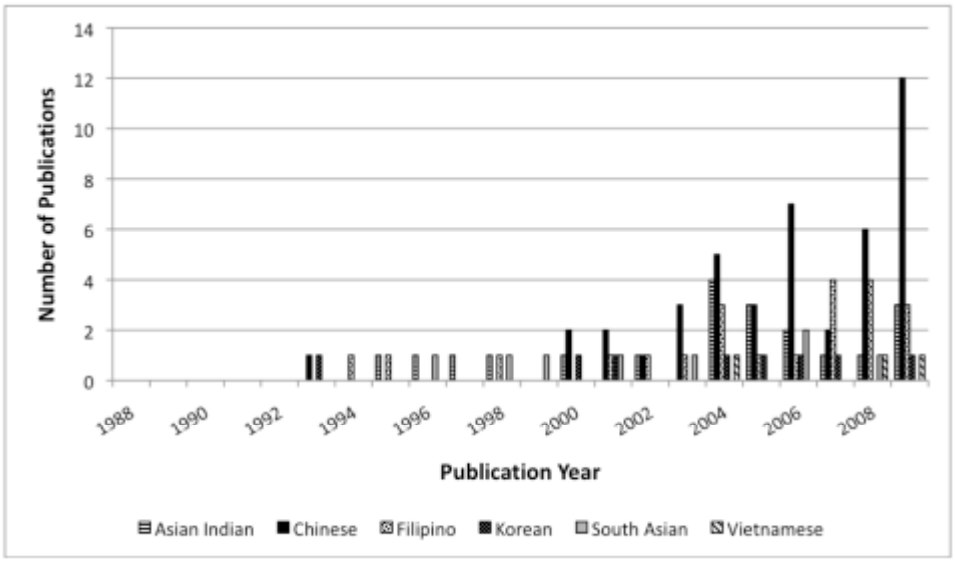
Legend 2. *Reports with electronic publication in 2009 and paper publication in 2010 were included

Fig. (2). Number of publications reporting on Asian groups, 1988 – 2009,* by Asian American sub-population.

Study Characteristics

Articles were identified for the following Asian subgroups: South Asian (n=8), Asian Indian (n=20), Chinese (n=44), Filipino (n=22), Korean (n= 8), and Vietnamese (n=3). Most articles reported on one Asian subgroup, however six reported on two or more Asian subgroups as defined for this review [2-7], hence the summation of articles by subgroup was greater than 97. In all studies, ethnicity was defined by participant self-report of ethnicity, origin, or ancestral origin. Although searches were conducted for studies with Bangladeshi, Bhutanese, Nepalese, Pakistani, or Sri Lankan individuals, no articles were found for these groups. Of the 97 articles in the systematic review, nearly half (n=46) were analyses of one of the following seven studies: Multi-Ethnic Study of Atherosclerosis [8-25] (MESA, n=18), Study of Women's Health Across the Nation [26-37] (SWAN, n=12), Filipino Women's Health Study [38-44] (n=7), Kōhala Health Research Project/Native Hawaiian Health Research Project [41, 45, 46] (NHHR, n=3), Behavioral Risk Factor Survey in Guam [47, 48] (BRFS, n=2), University of California San Diego (UCSD) Rancho Bernardo Study [49, 50] (n=2), and National Health Interview Survey [5, 7] (NHIS, n=2). Almost all articles reported cross-sectional data for the variables of interest; only two SWAN studies [27, 33] provided longitudinal data. Nationally representative data were sparse and limited to articles reporting NHIS data; however, several articles reported on studies with multi-center recruitment, including MESA (six centers throughout the U.S.: Baltimore, MD; Chicago, IL; Forsythe County, NC; Los Angeles, CA; New York City, NY; and St. Paul, MN) and the Diabetes Among Indian Americans (DIA) study [51] (seven urban sites: Houston, TX; Phoenix, AZ; Washington, DC; Boston, MA; San Diego, CA; Edison, NJ; and Parsippany, NJ). A quarter of all studies utilized random sampling methods (n=26).

The number of studies representing specific Asian subgroups is proportional to the population sizes of Asian subgroups in the U.S.; Chinese were represented in the most studies (47% of all studies, largest U.S. Asian subgroup) followed by South Asians and Filipinos (27% and 24%, respectively, the 3rd and 2nd largest U.S. Asian subgroups) (Fig. **2**). Additionally, the number of studies reporting data on Asian-specific subgroups increased from 1988-2009 (Fig. **3**), with the greatest number of publications with Chinese participants apparent after 2002. The observed sample sizes in the 97 articles ranged from 32 subjects to 4245 subjects. The mean age reported across studies ranged from 24 to 78 years. The ages of participants in the most common studies were 45-84 years in MESA, 40-55 in SWAN, 18 years and older in NHIS, 18 to 95 years in NHHR, and 40-76 years in the Filipino Women's Health Study. Prevalence estimates of interest were variable and wide-ranging across all subgroups. Only 20% of all articles reported prevalence data that were adjusted for age, sex, and/or other factors in the study sample or that were standardized for age, sex, and/or other factors to another population. Such data were provided for five Asian Indian [5, 51-54] articles, two Chinese [2, 5] articles, nine Filipino [2, 5, 38-41, 47, 50, 55] articles, two Korean [56, 57] articles, and one Vietnamese [58] article. None were reported for the South Asian category. Hereafter, reported values are crude unless otherwise noted. Of 32 articles providing prevalence of overweight and/or obesity, 63% (n=20) reported only conventional definitions for overweight or obesity (i.e., $25 \leq BMI < 30$, $BMI \geq 30$ kg/m^2) or similarly (e.g., $26 \leq BMI \leq 30$ kg/m^2). Five articles defined overweight and obesity according to 2004 WHO Asian-specific cut-points [59] (BMI 23.0 – 27.4 kg/m^2 and $BMI \geq 27.5$ kg/m^2, respectively) or similarly (obesity as $BMI \geq 27.8$ kg/m^2) [5, 51, 53, 60, 61]. Six studies defined overweight without an upper BMI bound (i.e., as $BMI \geq 23$; $BMI > 23$; $BMI > 25$; or $BMI \geq 25$ kg/m^2) [4, 62-66]. Over half (n=52) of all articles reported prevalence of diabetes, defining diabetes by one or more of the following methods: self-report (n=42, includes self-report of diagnosis or diabetes medication usage), fasting blood glucose (n= 32), two-hour glucose tolerance



Legend 3: *Reports with electronic publication in 2009 and paper publication in 2010 were included.

Fig. (3). Number of peer-reviewed publications reporting data on specific Asian groups by year*

(n=11), or random (nonfasting) blood glucose (n=1). Five articles did not provide the method used to assess diabetes [23, 67-70].

Summary of BMI, Overweight, Obesity, and Diabetes across Asian Subgroups

Among men and women combined, the lowest mean BMI reported was 22.1 kg/m^2 in South Asians [71], whereas the highest mean was reported in Filipino adults (26.8 kg/m^2) [46]. Among men, the lowest mean BMI was reported among young, Asian Indian men (22.8 kg/m^2) [54]; the highest mean was 25.9 kg/m^2 among Asian Indian immigrants to the San Francisco area [72, 73] and 25.7 kg/m^2 among Filipino men from Guam [48]. Among women, the lowest mean BMI was reported in Chinese community college students (19.4 kg/m^2) [6], and the highest mean was among Korean elderly women age 65 and greater (26.3 kg/m^2) [74].

According to NHIS data, which included Asian Indian, Chinese, and Filipino Asian subgroups, the highest proportions of overweight (23.0 ≤ BMI ≤ 27.4 kg/m^2) and obesity (BMI ≥ 27.5 kg/m^2) adjusted for age and sex were among Filipinos (46.5% overweight, 20.8% obese) and Asian Indians (46.7% overweight, 16.6% obese) [5]. Across all other studies combining men and women, the highest percent overweight (BMI 23-27.4 kg/m^2) was reported among Koreans (38.4%) [60] and the highest percent obesity (defined as BMI ≥ 25 kg/m^2) was reported among Filipinos (59%) [4]. Among studies reporting on both men and women, the lowest rate of overweight (25≤BMI≤29.9 kg/m^2) was among Asian Indians (12.8%) [75] and the lowest rate of obesity (BMI ≥ 30 kg/m^2) was reported for Vietnamese (2.1%) [58].

The prevalence of diabetes varied widely across articles. The lowest prevalence of diabetes was reported in South Asians (1%) [68], Chinese (3.96%) [64], and Vietnamese (5.3%, age-standardized) [58]. Reports for the greatest percent of diabetes included those for Filipinos (e.g., 36.4%, women in the Filipino Women's Health Study [42]) and Chinese (28%, 45 years or older with at least one CVD risk factor [4]). According to NHIS results, percent diabetes increased in overweight and even more in obesity across ethnicities studied. Comparing Asian subgroups (i.e., Asian Indian, Chinese, and Filipino) in a pooled NHIS analysis from 1997 to 2005, Asian Indians had the highest rates of diabetes in every category of BMI (age- and sex- standardized), compared to Chinese or Filipinos [5].

BMI, Overweight, Obesity, and Diabetes by specific Asian Subgroup

South Asians

Across the eight publications of South Asian samples, data were cross-sectional and unadjusted (Table **1**). The mean BMI for analyses of men and women combined ranged from 22.1-25.8 kg/m^2 [71, 76, 77]. Other studies provided mean BMI of 22-25 kg/m^2 for males [69, 71, 78] and 22.3-25 kg/m^2 for females [69, 78, 79]. Percent diabetes ranged from 1-11.6% [53, 68, 76]. Ivey and colleagues reported two studies (the California Health Interview Survey, CHIS, and the Cardiovascular Health Among Asian Indians Survey, CHAI) of South Asians in one publication [76]. CHIS recruited participants from a random-digit dial of households drawn from every county in California plus households from surname lists. Mean BMI was 24.5 kg/m^2, and 4% (n=37) reported diabetes. CHAI included South Asian adults from one of three areas within northern California using list-driven, surname-based recruitment (n=252 telephone participants; n=52 in-person participants). Here, mean BMI was 25.6 kg/m^2 (telephone participants) and 25.8 kg/m^2 (in-person participants). Self-reported diabetes was 11% (n= 27) for telephone participants and 10% (n=5) for in-person participants. All other studies about South Asians used convenience samples. The largest of these studies examined South Asians living in Dallas; this study reported mean BMI at 24.9 kg/m^2 (n=616 participant without diabetes, mean age 42 years) [77]. In another study of South Asians aged 18-30 years, mean BMI (22.1 kg/ m^2) was similar to European

Table 1. Results of a Systematic Review of Mean BMI, Percent Overweight (ov)/Obese (ob), and Prevalence of Diabetes in Asians: South Asian References (n=8)

Reference	City, State	Sample Size	Mean Age in Years ± SD	Mean BMI in kg/m^2 ± SD	Definition of ov, ob by BMI (kg/m^2)	Ov, ob, %	Diabetes, %
Anand 1998 [68]	***[a]	141[a]	47[a]	***	***	***	1[a, c]
	Chicago, IL[b]	255[b]	46[b]	***	***	***	11.3[b, c]
Chandalia 2008 [69]	Dallas, TX	418 (men) 331 (women)	42 ± 15 (men) 42 ± 14 (women)	25 ± 15 (men) 25 ± 4 (women)	***	***	***
Chandalia 2003 [78]	Dallas, TX	82 (men)	31 ± 12 (men)	23.9 ± 3.1 (men)	***	***	***
Enas 1996 [53]	***	1688 (total) 1131 (men) 557 (women)	46.4 ± 7.5 (men) 42.9 ± 7.4 (women) 48.0 ± 5.5 (men ≥ 40 years)	***	ob: BMI≥27.8	ob: 6.7 (men≥40 years)	7.6 (total)[d] 9.0 (men)[d, e] 6.1 (women)[d,e]
Ivey 2006 [76]	CA counties / northern CA	769[f]	***	24.5 ± 5.5[f]	***	***	4[f,g]
	CA counties / northern CA	252[h] 52[i]	***	25.6 ± 5.2[h] 25.8 ± 6.0[i]	***	***	11[h,g] 10[i,g]
Kalhan 2001 [71]	Cleveland area, OH	32	23.8 ± 2.0	22.1 ± 3.0	***	***	***
Kamath 1999 [79]	Chicago, IL	47 (women)	27.5 ± 5.6 (women)	22.6 ± 3.2 (women)	***	***	***
Radha 2006 [77]	Dallas, TX	616[j]	42 ± 13[j]	24.9 ± 3.7[j]	***	***	***

*** data not included or specified
[a] The first of two studies reported in Anand 1998 of the Coronary Artery Disease in Asian Indians (CADI) study
[b] The second of two studies reported in Anand 1998
[c] Estimate method not specified
[d] Based on previous diagnosis or use of insulin or oral hypoglycaemic agents
[e] Adjusted for age
[f] The first of two studies reported in Ivey 2006, the California Health Interview Study (CHIS) which used population-based random sampling
[g] Based on self-report
[h] The second of two studies reported in Ivey 2006, the phone portion of the Cardiovascular Health Among Asian Indians Survey (CHAI) which used population-based sampling
[i] The second of two studies reported in Ivey 2006, the in-person interview of the Cardiovascular Health Among Asian Indians Survey (CHAI) which used population-based sampling
[j] Portion of total sample without diabetes

Americans (23.7 kg/m^2); however South Asians had statistically higher ($p<0.05$) mean fasting blood glucose and family history of diabetes [71]. These findings are supported by another study among females with no history of diabetes, where mean fasting glucose was elevated (102.7 mg/dl) [79].

Asian Indians

All 20 articles identified for the Asian Indian subgroup were cross-sectional studies (Table **2**). Oza-Frank, *et al*. 2009 [5] provided the largest sample of Asian Indians (n= 1357) with NHIS representing 1,234,233 individuals in the U.S.. The DIA study reported on 1038 Asian Indian adults (18 years and older) residing in seven U.S. urban sites [51]. While NHIS studies did not provide mean BMI, the DIA study reported a mean of 25.4 kg/m^2, adjusted for age and sex. In addition to the DIA study, eleven articles reported mean BMI for men and women combined with estimates ranging from 22.4 - 26.1 kg/m^2 [54, 61, 70, 72, 73, 75, 80-84]. The lower and upper values of this range were estimated by convenience samples, with the lower value among young, healthy volunteers (n=49) [54] and the upper value reported both among Asian Indians originally from the state of Gujarat living in Atlanta, Georgia (n=1046) [83] and among Asian Indian immigrants aged 29-59 in the San Francisco Bay area (n = 56) [72, 73]. Some articles stratified BMI by sex or studied only one gender, and the reported estimates for men and for women were similar, ranging from 22.8 to 25.9 kg/m^2 for men [51, 52, 54, 72, 73, 75, 82, 85-87] and 21.7 to 26.5 kg/m^2 for women [51, 52, 75, 82, 88].

Two articles reported the prevalence of overweight using Asian-specific cut-points. In NHIS, 46.7% (age- and sex-standardized) were overweight [5]. Misra, *et al.* 2010 reported 25% overweight among DIA participants (age- and sex- adjusted) [51]. The prevalence of overweight in men and women combined using other definitions for overweight ranged from 12.8-43.0% [7, 51, 70, 75, 80, 81, 89]. Three studies reported prevalence of obesity using WHO criteria

Table 2. Results of a Systematic Review of Mean BMI, Percent Overweight (ov)/Obese (ob), and Prevalence of Diabetes in Asians: Asian Indian references (n=20)

Reference	City, State	Sample Size	Mean Age in Years ± SD	Mean BMI in kg/m^2 ± SD	Definition of ov, ob by BMI (kg/m^2)	Ov, ob, %	Diabetes, %
Abate 2004 [85]	***	79 (men)	31 ± 12 (men)	24 ± 3 (men)	***	***	***
Abate 1995 [86]	***	93 (men)	47 ± 6 (men)	24.8 ± 3.1 (men)	***	***	***
Balasubramanyam 2008 [80]	Houston, TX	143	50.3 ± 13.8	25 ± 5.00	ov: 25<BMI<30 ob1: BMI≥30 ob2: BMI≥25	ov: 31 ob1: 11 ob2: 43	18[a]
Bhalodkar 2005 [88]	***	119 (women)	47.9 ± 11.2 (women)	24.0 ± 4.7 (women)	***	***	***
Chuang 1998 [52]	***	110 (total) 64 (men) 46 (women)	45.9 ± 8.7 (men) 44.3 ± 8.6 (women)	24.0 ± 2.7 (men) 23.7 ± 3.1 (women)	***	***	7.5 (total)[b] 6.6 (men)[b] 8.9 (women)[b]
Ivey 2004 [84]	Northern CA cities	304	40	25.7	ov & ob: BMI>25[c]	ov & ob: 46.4	10.6 [b]
Jonnalagadda 2007 [82]	Canton, MI	101 (total) 44 (men) 57 (women)	53 ± 13 (men) 55 ± 11 (women)	25.5 (total) 25.1 ± 3.1 (men) 25.8 ± 4.4 (women)	***	***	***
Jonnalagadda 2005 [81]	Metropolitan Atlanta, GA	226	58 ± 6	24.9 ± 3.3	ov: 25≤BMI≤29.9 ob: BMI>30	ov: 35 ob: 5	18[b]
Jonnalagadda 2002 [89]	Metropolitan Atlanta, GA	237	***	***	ov & ob: BMI>25[c]	ov & ob: 43	***
Kamath 1997 [87]	***	187 (men)	46 ± 9.3 (men)	23.6 (men)	ov: 26≤BMI≤30 ob: BMI>30	ov: 24 (men) ob: 2.2 (men)	8.8 (men)[b]
Misra 2010 [51]	7 suburban sites in United States	1038 (total)[d] 609 (men) 429 (women)	45.7 ± 12.8 (total)	25.4 ± 3.7 (total) 25.3 ± 3.3 (men) 25.6 ± 4.4 (women)	ov1: 25<BMI <30 ov2: 23.0≤BMI≤27.4 ob1: BMI≥30 ob2: BMI≥27.5	ov1: 38 (total) ov2: 25 (total) ob1: 11 (total) ob2: 49.8 (total)	17.4 (total)[e] 20.0 (male)[e] 13.8 (female)[e] 14.0 (known)[e] 3.4 (newly diagnosed)[e] 3.9 (among 20-39 years)[e] 17.1 (among 40-59 years)[e] 31.2 (among ≥ 60 years)[e]
Misra 2006 [73]	San Francisco Bay Area, CA	56 (total) 31 (men)	43.4 ± 6.9 (total) 43.7 ± 7.1 (men)	26.1 ± 3.7 (total) 25.9 ± 3.1 (men)	***	***	***
Misra 2005 [72]	San Francisco Bay Area, CA	56 (total) 31 (men)	43.4 ± 6.9 (total) 43.7 ± 7.1 (men)	26.1 ± 3.7 (total) 25.9 ± 3.1 (men)	***	***	***
Misra 2000 [75]	***[f]	261 (total)	46.1 ± 7.4 (total)	24.0 (total) 24.3 (men) 23.3 (women)	ov: 25≤BMI≤29.9 ob: BMI>30	ov: 12.8 (total) ov: 14.2 (men) ov: 9.4 (women) ob: 7.4 (total) ob: 8.9 (men) ob: 4.1 (women)	***

Table 2. contd….

Reference	City, State	Sample Size	Mean Age in Years ± SD	Mean BMI in kg/m^2 ± SD	Definition of ov, ob by BMI (kg/m^2)	Ov, ob, %	Diabetes, %
Mooteri 2004 [70]	***	489[g]	49 ± 12	24.0 ± 3.5	ob: BMI>30	ob: 6	9[h]
Oza-Frank 2009 [5]	United States, 1997-2005 [i]	1357	37.6 (SE 0.4)	***	ov1: 23.0≤BMI≤27.4 ov2: 25.0≤BMI≤29.9 ob1: BMI≥27.5 ob2: BMI≥30	ov1: 46.7, SE 1.8[j] ov2: 34.1, SE 1.6[j] ob1: 16.6, SE 1.4[j] ob2: 6.7, SE 0.9[j]	6.5, SE 1.9[b, j, k] 8.3, SE 1.7 (ov1)[b, j] 8.8, SE 1.8 (ov2)[b, j] 19.4, SE 3.5 (ob1)[b, j] 32.9, SE 4.4 (ob2)[b, j]
Petersen 2006 [54]	***	49 (total) 31 (men)	28.7 ± 8.3 (total) 30.0 ± 8.7 (men)	22.4 ± 2.3 (total) 22.8 ± 2.2 (men)	***	***	***
Venkataraman 2004 [83]	Atlanta, GA	1046	52.8 ± 11.3	26.1 ± 4.7	***	***	18.1[b]
Yagalla 1996 [61]	***	153	47.4 ± 6.4	24.6 ± 2.7	ob: BMI≥27.8	ob: 8	***
Ye 2009 [7]	United States, 2003-2005[i]	534	***	***	ob: BMI≥30	ob: 6.1	8.2[b]

*** Data not included or specified
[a] Based on fasting overnight blood glucose >100mg/dl – or – self diagnosed
[b] Based on self-report
[c] Reported as overweight in publication
[d] Sample from the Diabetes among Indian Americans (DIA) study. Directories for random sampling were created at each site through compilations of several sources. Five thousand were selected from this database (n=43,150)
[e] Diabetes diagnosed by fasting blood glucose ≥ 126 mg/dl or self-report of previously diagnosed diabetes
[f] Survey participants were invited from a directory of a national Gujarati Association in the United States
[g] Portion of total sample without coronary artery disease
[h] Estimate method not specified
[i] Participants from the National Health Interview Survey, a U.S. nationally representative survey of non-institutionalized adults (18 and older)
[j] Age and sex standardized to the 2000 U.S. population
[k] Among those with BMI 18.5-22.9 kg/m^2

for Asian populations; obesity prevalence in these studies ranged from 8% to 49.8% [5, 51, 61].

The prevalence of diabetes was reported in eleven articles (Table **2**). In the DIA study, prevalence of diabetes for adults aged ≥20 was 17.4% (n=181), where 13.9% were known cases and 3.5% were previously undiagnosed (estimates age- and sex-adjusted) [51]. Stratifying by WHO Asian-specific BMI categories, NHIS diabetes estimates (age- and sex- standardized) were 6.5% among normal weight participants (BMI 18.5-22.9 kg/m^2); 8.3% among overweight participants (BMI 23.0-27.4 kg/m^2); and 19.4% among obese participants (BMI ≥ 27.5 kg/m^2) [5]. The lowest prevalence of diabetes was reported among a sample of 110 physicians and their adult family members aged 20 to 62 years (men: 6.6%; women: 8.9%; total: 7.5%) [52]. The largest reported prevalence of diabetes for men and women (32.9%, age- and sex- standardized) was reported in NHIS among Asian Indians with BMI ≥ 30 kg/m^2 [5].

Chinese

More articles (n=44) presented information about the Chinese subgroup compared to any other Asian subgroup in this systematic review (Table **3**). The only nationally representative samples identified in the systematic search for Chinese were NHIS samples [5, 7]. In the pooled (1997-2005) NHIS analysis, mean overweight was 38.2% (age- and sex-standardized), and mean obesity was 8.8% (age- and sex-standardized) as per WHO Asian-specific definitions [5]. This was the only study of Chinese Americans that used WHO definitions for overweight and obesity. In MESA, percent overweight (BMI 25-29.9 kg/m^2) was between 25-40% depending on age [13]. Furthermore, 4.5% were obese (BMI ≥ 30 kg/m^2) [10], an estimate similar to NHIS results when using non-Asian specific cut-points (NHIS 4.2%, age- and sex- standardized) [5]. In Hawaii, the Kidney Early Evaluation Program (KEEP-2) study contained 15% overweight and 47% obese volunteers as defined by the WHO International Obesity Task Force in 2000 (BMI≥23 kg/m^2 and BMI≥25 kg/m^2 respectively) [4].

Sex-specific estimates of percent overweight and obese were provided in a variety of ways across studies [3, 6, 34, 63, 90]. The highest estimates for overweight were from a subset of the New York City Chinese Health Study (NYC CHS), a population-based study of 55-75 year olds; the study reported 33% overweight (BMI = 25-29.9 kg/m^2) among men and 27.9% overweight among women [90]. This was the only study that reported prevalence of overweight for men alone. The lowest estimates for overweight among

Table 3. Results of a Systematic Review of Mean BMI, Percent Overweight (ov)/Obese (ob), and Prevalence of Diabetes in Asians: Chinese References (n=44)

Reference	City, State	Sample Size	Mean Age in Years ± SD	Mean BMI in kg/m^2 ± SD	Definition of ov, ob by BMI (kg/m^2)	Ov, ob, %	Diabetes, %
Multi-Ethnic Study of Atherosclerosis							
Allison 2009 [9]	[a]	803	62.3 ± 10.3	24.0 ± 3.3	***	***	15.2[b]
Allison 2009 [8]	[a]	258	65 ± 10	24 ± 3	***	***	15[b]
Bahrami 2008 [10]	[a]	803	62.3 ± 10.3	24.0 ± 3.3	ob: BMI≥30	ob: 4.5	15.2[b]
Bertoni 2006 [11]	[a]	651	***	***	***	***	14.4[c]
Bild 2005 [12]	[a]	803	62.9 ± 10.3	24.0 ± 3.3	***	***	15.7[d]
Burke 2008 [13]	[a]	803	***	23.9 (women) 24.1 (men)	ov: 25.0≤BMI≤29.9 ob: BMI>30.0	ov: 33 (total)[e] ob: 5 (total)[e]	***
Colangelo 2009 [14]	[a]	388 (men)	***	***	***	***	15 (men)[b]
Diez Roux 2005 [15]	[a]	768 (non-U.S.-born)	62.3 (non-U.S.-born)	23.9 (non-U.S.-born)	***	***	14.3 (non-U.S.-born)[d]
Duprez 2009 [16]	[a]	374 (men) 395 (women)	62.3 ± 10.2 (men) 62.2 ± 10.4 (women)	24.0 ± 3.1 (men) 23.9 ± 3.5 (women)	***	***	16 (men)[b] 15 (women)[b]
Gao 2008 [17]	[a]	790	62.9	24.0	***	***	***
Kandula 2008 [18]	[a]	737	62.8 ± 10.2	23.9 ± 3.3	***	***	13.3[b]
Katz 2006 [19]	[a]	801 (total) 388 (men) 413 (women)	***	***	***	***	15.7 (total)[b, f] 16.5 (men)[b, f] 15.0 (women)[b, f]
Klein 2006 [20]	[a]	727	62.4 ± 10.2	24.1 ± 3.3	***	***	15.3[c]
Kramer 2004 [21]	[a]	803	62.9 ± 10.3	24.0 ± 3.3	***	***	14[c]
Ouyang 2009 [22]	[a]	272	65.6 ± 9.1	24.1 ± 3.7	***	***	18.4[b]
Palmas 2008 [23]	[a]	790	62.3 ± 10.3	23.9 ± 3.3	***	***	14.7[g]
Paramsothy 2009 [24]	[a]	695	61.8 ± 10.4	23.8 ± 3.3	***	***	***
Wong 2006 [25]	[a]	724	61.8 ± 10.2	24.1 ± 3.3	***	***	14.5[b]
Study of Women's Health Across the Nation							
Everson-Rose, 2004 [27][h]	Oakland, CA area	210 (women)	46.5 ± 2.6 (women)	23.2 ± 3.8 (women)	***	***	2.9 (incident diabetes, women)[i]
Gold, 2000 [28]	Oakland, CA area	546 (women)	***	***	ob: BMI≥27[j]	ob: 9.5 (women)	***
Greendale, 2003 [29]	Oakland, CA area	250 (women)	46.5 ± 2.6 (women)	23.3 ± 3.9 (women)	***	***	***
Habel, 2007 [30]	Oakland, CA area	179 (women)	***	***	ov: 24.2≤BMI≤28.2 ob:28.3≤BMI≤55.8[j]	ov: 23 (women) ob: 11 (women)	***

Table 3. contd….

Reference	City, State	Sample Size	Mean Age in Years ± SD	Mean BMI in kg/m^2 ± SD	Definition of ov, ob by BMI (kg/m^2)	Ov, ob, %	Diabetes, %
Kelley-Hedgepeth, 2008 [31]	Oakland, CA area	244 (women)	46.7 (women)	22.5 (women)	***	***	2.2 (women)[b]
Lasley, 2002 [32]	Oakland, CA area	228 (women)	46.43 ± 2.54 (women)	23.17 ± 3.94 (women)	***	***	***
Lo, 2006 [33][h]	Oakland, CA area	151 (women)	***	***	***	***	3 (women)[b]
Matthews, 2005 [34]	Oakland, CA area	231 (women)	46.6 ± 2.6 (women)	23.2 ± 3.9 (women)	ov: 25≤ BMI<30 ob: BMI≥30	ov: 17.0 (women) ob: 4.4 (women)	***
Matthews, 2001 [26]	Oakland, CA area	562 (women)	***	22.90, SE 0.15 (women)	ob: BMI ≥ 30	ob: 3.56 (women)	***
Sowers, 2006 [36]	Oakland, CA area	151 (women)	46.0 ± 2.4 (women)	23.4 ± 4.2 (women)	***	***	***
Sowers, 2003 [35]	Oakland, CA area	220 (women)	47 ± 2.7 (women)	23.1 ± 3.9 (women)	***	***	***
Torrens, 2004 [37]	Oakland, CA area	210 (women)	46 ± 2.7 (women)	23.1 ± 3.8 (women)	***	***	***
National Health Interview Survey[j]							
Oza-Frank, 2009 [5]	United States, 1997-2005	1510	40.7 (SE 0.6)	***	ov1: 23.0≤BMI≤27.4 ov2: 25.0≤BMI≤29.9 ob1: BMI≥27.5 ob2: BMI≥30	ov1: 38.2, SE 1.3[l] ov2: 20.6, SE 1.1[l] ob1: 8.8, SE 0.8[l] ob2: 4.2, SE 0.6[l]	2.2, SE 0.7 [l, m, n] 3.8, SE 0.8 (ov1)[l, m] 5.2, SE 1.5 (ov2)[l, m] 11.2, SE 3.2 (ob1)[l, m] 16.8, SE 4.3 (ob2)[l, m]
Ye, 2009 [7]	United States, 2003-2005	559	***	***	ob: BMI≥30	ob: 4.2	5.5[m]
Other studies with Chinese participants							
Babbar, 2006 [91]	New York City, NY	300 (women)	63.0 ± 8.2 (women)	24.7 ± 4.0 (women)	***	***	***
Chen, 2009 [63]	San Francisco Bay Area, CA	65 (women)	***	23.1 ± 4.2 (women)	ov & ob: BMI>25[o]	ov & ob: 23.3 (women)	***
Cotler, 2009 [67]	Chicago, IL	2,457	55 ± 18	24 ± 4	ob: BMI>25	ob: 36	12[g]
Gomez, 2004 [2]	San Francisco, CA[p]	263 (total)	***	***	ov: 26≤BMI≤30 ob: BMI>30[j]	ov: 18.4[q] ob: 4.7[q]	6.4[m, q]
Hung, 2009 [64]	New York City, NY	2537 (total)	***	***	ov & ob: BMI>23[r]	ov & ob: 5.93, SE 0.61	3.96, SE 0.53[m]
Kim KK, 1993 [3]	Chicago, IL	169 (total) 59 (men) 110 (women)	74.6 (total)	23.2 ± 3.7 (men) 23.3 ± 3.9 (women)	ob: BMI>30.0	ob: 3.6 (men) ob: 4.7 (women)	***
Lauderdale, 2003 [108]	Chicago, IL	469	71	***	ov: 24.0≤BMI<26.5 ob: BMI≥26.5[j]	ov: 26 ob: 23	***
Maskarinec, 2001 [109]	Island of Oahu, HI	73 (women)	56.7 (women)	22.8 (women)	***	***	***

Table 3. contd….

Reference	City, State	Sample Size	Mean Age in Years ± SD	Mean BMI in kg/m^2 ± SD	Definition of ov, ob by BMI (kg/m^2)	Ov, ob, %	Diabetes, %
Maskarinec, 2000 [110]	Island of Oahu, HI	73 (women)	56.7 (women)	22.8 (women)	***	***	***
Mau, 2007 [4]	HI[s]	81	***	***	ov: 23≤BMI<25[t] ob: BMI≥25	ov: 15 ob: 47	28[u]
Parikh, 2009 [90]	New York City, NY	517 (total)[v] 336 (men) 181 (women)	63.5, SE .38 (total) 64.3, SE .40 (men) 62.4, SE .61 (women)	23.3 (total) 23.5 (men) 23.1 (women)	ov: BMI 25.0-29.9 ob: BMI≥30	ov: 30.8 (total) ov: 33.0 (men) ov: 27.9 (women) ob: 2.4 (total) ob: 3.5 (men) ob: 0.9 (women)	***
Yates, 2004 [6]	HI	45 (women)	***	19.35 ± 3.51 (women)	ob: BMI>30	ob: 2 (women)	***

*** Data not included or specified
[a] Baltimore, MD; Chicago, IL; Forsythe County, N.C.; Los Angeles, CA; New York, NY; and St. Paul, MN
[b] Based fasting glucose ≥ 126 mg/dl, or use of hypoglycemic medication
[c] Based on self-report, fasting glucose ≥ 126 mg/dl, or use of hypoglycemic medication
[d] Based fasting glucose > 126 mg/dl, or use of hypoglycemic medication
[e] Estimates based on figure
[f] Percent diabetes calculated by reviewer
[g] Estimation method not specified
[h] Longitudinal analysis
[i] Based on self-report of diabetes treatment at any annual follow-up visit or based on a fasting glucose level of ≥ 126 mg/dl at the first and/or third follow-up
[j] Authors reported a distribution of BMI rather than overweight or obesity explicitly
[k] U.S. nationally representative survey of non-institutionalized adults (18 and older)
[l] Age and sex standardized to the 2000 U.S. population
[m] Based on self-report
[n] Among those with BMI 18.5-22.9 kg/m^2
[o] Reported as overweight in the publication
[p] Hayward, Oakland, San Francisco, Santa Clara, and South San Francisco, CA
[q] Adjusted for age and sex
[r] Reported as BMI >23 kg/m^2 for overweight and BMI >25 kg/m^2 for obesity in the publication
[s] Hawaii site for the Kidney Early Evaluation Program (KEEP-2)
[t] Overweight was reported as BMI ≥23 in the publication with a prevalence of 15%
[u] Based on self-reported history or a random blood glucose value ≥ 200 mg/dl (nonfasting)
[v] Sample from New York City Chinese Health Study (NYC CHS), which used a complex multi-stage systematic stratified sampling design. May not be representative of frail elderly and the oldest old

women were reported in the SWAN study; 17.0% of women in this study were overweight (25≤ BMI >30 kg/m^2) [34]. Only two estimates for percent obesity were found, and both were similar (3.5%, BMI ≥ 30 kg/m^2) and 3.6%, BMI >30.0) [3, 90]. In women, obesity ranged from 0.9% to 11% [3, 6, 26, 28, 30, 34, 90].

Mean BMI ranged from 23.3 kg/m^2 (Chinese participants aged 55-75 years subset from the NYC CHS) [90] to 25.8 kg/m^2 (U.S.-born Chinese aged 45-84 years at baseline from the MESA study) among men and women [15]. Among men only, mean BMI ranged from 23.2 kg/m^2 in elderly Chicago residents [3] to 24.1 kg/m^2 in MESA participants [13]. Among women, the lowest mean BMI (19.4 kg/m^2) was reported in a convenience sample of community college students [6] and the greatest (24.7 kg/m^2) in a convenience sample of postmenopausal women from New York City's Chinatown [91]. Mean BMI in SWAN was 22.5 - 23.4 kg/m^2 [3, 26, 27, 29, 31, 32, 35-37].

Diabetes prevalence estimates varied across studies. In a pooled NHIS analysis (1997-2005), 2.2% of normal weight Chinese (BMI 18.5-22.9 kg/m^2), 3.8% of overweight Chinese (BMI 23.0-27.4 kg/m^2), and 11.2% of obese Chinese (BMI ≥ 27.5 kg/m^2) had self-reported diabetes (all data age- and sex-standardized to the 2000 U.S. population) [5]. Those with BMI ≥ 30 kg/m^2 had 16.8% diabetes. Across all articles in the Chinese subgroup, the greatest prevalence diabetes was reported at 28% among Chinese participants in Hawaii, based on self-report or random, nonfasting blood glucose levels at 200 mg/dl or greater [4]. In MESA, 15.2% had diabetes based on a definition that included self-report, fasting glucose ≥ 126 mg/dl, or by use of hypoglycemic medication [9, 10].

Filipino

Among the 22 publications with Filipinos, all data were cross-sectional (Table **4**). Seven publications reported population-based data from NHIS [5, 7], BRFS in Guam [47, 48], or the Kōhala Health Research Study/Native Hawaiian Health Research Project (NHHR) in rural North Kōhala, Hawaii [41, 45, 46]. In NHIS (1997-2005), 46.5% of individuals were overweight and 20.8% of individuals were obese (n = 1485, age- and sex- standardized) using WHO

Table 4. Results of a Systematic Review of Mean BMI, Percent Overweight (ov)/Obese (ob), and Prevalence of Diabetes in Asians: Filipino References (n=22)

Reference	City, State	Sample Size	Mean Age in Years ± SD	Mean BMI in kg/m^2 ± SD	Definition of ov, ob by BMI (kg/m^2)	Ov, ob, %	Diabetes, %
The University of California San Diego Filipino Women's Health Study							
Araneta 2007 [40]	San Diego area, CA	136 (women)	54.2 (women)	24.3 (women)[a]	***	***	***
Araneta 2006 [41][b]	San Diego, CA	446 (women)	57.6, 95% CI: 56.7, 58.5 (women)	25.4, 95% CI: 25.0, 25.8 (women)[a]	ob1: BMI≥25 ob2: BMI≥30	ob1: 49.2 (women)[a] ob2: 9.3 (women)[a]	31.6 (women)[a, c] 24.9 (women)[a, c]
Araneta 2005 [39]	San Diego area, CA	181 (women)	64.4 (women)	25.5 (women)[a]	***	***	32.1 (women)[a, c]
Araneta 2004 [38]	San Diego area, CA	181 (women)	64.4 ± 6.0 (women)	25.6 ± 3.4 (women)[a]	***	***	32.6 (women)[a, c]
Araneta 2002 [42]	San Diego area, CA	294 (women)	59.7 ± 5.2 (women)	25.6 ± 3.5 (women)	***	***	36.4 (women)[c]
Magno 2008 [43]	San Diego area, CA	211 (women)[d]	57.3, SE 0.68 (women)	25.1, SE0.23 (women)	***	***	27.5 (women)[c]
Wong 2008 [44]	San Diego area, CA	163 (women)	59.3 - 60 (women)[e]	25.1 – 26.3 (women))[e, a]	***	***	34.4 (women)[c]
Kōhala Health Research Project / Native Hawaiian Health Research Project							
Araneta 2006 [41][b]	North Kōhala, HI	109 (women)	57.9, 95% CI: 56.0, 59.8 (women)	26.0, 95% CI: 24.8, 26.5 (women)[a]	ob1: BMI≥25 ob2: BMI≥30	ob1: 50.5 (women)[a] ob2: 20.1 (women)[a]	24.9 (women)[a,c]
Grandi-netti 2007 [45]	North Kōhala, HI	186	53.7 ± 16.2	26.1 ± 5.8	***	***	19.35[f]
Kim 2008 [46]	North Kōhala, HI	261	50.0 ± 16.3	26.8 ± 5.7	***	***	20.3[g] 30.9 [g] (among those with age ≥50 years) 8.3[g] (among those with age <50 years)
The University of California San Diego (UCSD) Rancho Bernardo Study							
Araneta 2010 [49]	San Diego, CA	152 (women)	59.5 (women)	25.4 (women)	***	***	33.6 (women)[c]
Morton 2003 [50]	San Diego, CA	285 (women)	59.9, 95% CI 59.3, 60.5 (women)	25.4, 95% CI: 24.0 - 25.9 (women)[a]	***	***	***
Behavioral Risk Factor Survey (BRFS)[h] – Guam							
Pinhey 1995 [47]	Guam	342[i]	*** [j]	23.09[a]	***	***	***
Pinhey 1994 [48]	Guam	115 (total) 49 (men) 66 (women)	48.1 ± 15.9 (men) 41.6 ± 12.6 (women)	25.7 ± 3.8 (men) 22.8 ± 4.4 (women)	ob: BMI ≥ 27	Ob: 21.2 (total)	***

Table 4. contd….

Reference	City, State	Sample Size	Mean Age in Years ± SD	Mean BMI in kg/m^2 ± SD	Definition of ov, ob by BMI (kg/m^2)	Ov, ob, %	Diabetes, %
National Health Interview Survey (NHIS)[k]							
Oza-Frank 2009 [5]	United States, 1997-2005	1485	41.2, SE 0.4	***	ov1: 23.0≤BMI≤27.4 ov2: 25.0≤BMI≤29.9 ob1: BMI≥27.5 ob2: BMI≥30	ov1: 46.5, SE 1.7[l] ov2: 34.5, SE 1.4[l] ob1: 20.8, SE 1.3[l] ob2: 10.2, SE 1.0[l]	5.9, SE 3.7 [l, m, n] 3.7, SE 0.7 (ov1)[l, m] 6.2, SE 1.1 (ov2)[l, m] 11.3, SE 2.0 (ob1)[l, m] 10.9, SE 3.0 (ob2)[l, m]
Ye 2009 [7]	United States, 2003-2005	633	***	***	ob: BMI≥ 30	Ob: 13.2	6.1[m]
Other studies with Filipino participants							
Cuasay 2001 [55]	Metropolitan Houston, TX	831	46.1 ± 12.0	24.6 ± 3.6	***	***	16.1. 95% CI: 13.5, 18.7 (total)[o, p] 13.1, 95% CI: 10.0, 16.2 (women)[p, q] 19.7, 95% CI: 15.1, 24.3 (men)[p, q] 15.1, 95% CI: 12.4-17.8 (among BMI≤30)[p, q] 30.0, 95% CI: 16.6-43.4 (among BMI>30)[p, q]
Gomez 2004 [2]	San Francisco, CA[r]	268 (total)	***	***	ov: 26≤BMI≤30[s] ob: BMI > 30[s]	ov: 29.2 ob: 8.6	21.2 [m, t]
Guerrero 2008 [111]	Guam	61 (total) 33 (women)	***	25.9 (total) 24.4 ± 3.6 (women)	ov: 25.0≤BMI≤29.9 ob: BMI ≥ 30	ov: 30.3 (female) ob: 9.1 (female) ob: 20 (total)	***
Langenberg 2007 [112]	North San Diego, CA	389 (women)	58.7 ± 9.4 (women)	25.3, 95% CI: 24.9, 25.6 (women)	ob: not defined	ob: 9.8, 95% CI: 6.8, 12.7 (women)	31.4, 95% CI: 26.7, 36.0 (women)[c]
Mau 2007 [4]	HI[u]	134	***	***	ov: 23≤BMI<25[v] ob: BMI≥25	ov: 15 ob: 59	20[w]
Novotny 1998 [113]	HI	74 (women)	***[x]	23.8 ± 4.5 (women)	***	***	***
Yates 2004 [6]	HI	59 (women)	***	21.71 ± 3.86 (women)	***	***	***

Table 4. contd…

*** Data not included or specified
[a] Adjusted for age
[b] Araneta 2006 provides separate estimates from two studies (in California and in Hawaii) and it is listed under two sections: The University of California San Diego Filipino Women's Health Study and the Kōhala Health Research Project / Native Hawaiian Health Research Project
[c] Based on 1999 World Health Organization criteria: fasting plasma glucose ≥ 126 mg/dl; 2-hour postchallenge glucose ≥ 200 mg/dL; history of type 2 diabetes diagnosed by a physician; or history of treatment with oral hypoglycemic agent or insulin
[d] Study reported additional data on 55 women with cardiovascular disease but these data are not included here due to exclusion criteria
[e] Mean age/BMI stratified by those with and without diabetes
[f] Based on 1998 WHO criteria for diabetes and abnormalities of glucose regulation
[g] Based on 1998 WHO criteria for diabetes: 2-hour plasma glucose 200 mg/dl; or fasting plasma glucose ≥ 126 mg/dl
[h] Survey representative of the non-institutionalized, adult (18 and older) population in Guam
[i] Portion of total sample without hypertension
[j] Aged 30 years and older
[k] U.S., nationally representative survey of non-institutionalized, adults (18 and older)
[l] Age and sex standardized to the 2000 U.S. population
[m] Based on self-report
[n] Among those with BMI 18.5-22.9 kg/m^2
[o] Unweighted, unadjusted prevalence
[p] Based on subjects' self-report. Presence of diabetes confirmed with questions on the questionnaire regarding the year and/or individuals age at diagnosis of diabetes, blood and OGTT, therapy used, frequency of blood tests, and doctors' visits
[q] Weighted prevalence
[r] Hayward, Oakland, San Francisco, Santa Clara, & South San Francisco, CA
[s] Authors reported a distribution of BMI rather than overweight or obesity explicitly
[t] Adjusted for age and sex
[u] Hawaii site for Kidney Early Evaluation Program (KEEP-2)
[v] Overweight was reported as BMI ≥ 23 in publication with a prevalence of 15%
[w] Based on prior history or a random blood glucose value ≥ 200mg/dL (non-fasting)
[x] Women were between 25 and 35 years of age, mean age not provided

Asian specific definitions for overweight and obesity [5]. While data from NHIS 2003-2005 indicate that 13.2% of Filipinos were obese (BMI ≥ 30 kg/m^2) [7], pooled NHIS data from 1997 – 2005 show that 10.2% were obese [5], reflecting the increase in obesity over time. The lowest mean BMI among Filipinos was reported in Guam at 23.1 kg/m^2 (age-adjusted) for men and women combined, 25.7 kg/m^2 for men only, and 22.8 kg/m^2 for women only [47, 48]. Mean BMI among men and women from the NHHR project ranged from 26.0 kg/m^2 to 26.8 kg/m^2, with the latter estimate as the greatest estimate in the Filipino subgroup [41, 45, 46]. Among women, mean BMI was 21.7 kg/m^2 among community college students in Hawaii [6], between 24.3 kg/m^2 (age-adjusted) to 25.6 kg/m^2 among 40 to 86 year olds from San Diego county [38-44], 25.4 kg/m^2 (age-adjusted) among postmenopausal women in northern San Diego County [49, 50], and 26.0-26.8 kg/m^2 in the NHHR project [41, 45, 46]. Only one estimate was provided for men (mean BMI 25.7 kg/m^2) [48].

From 2003-2005, 6.1% Filipinos had diabetes in NHIS [7]. Pooled NHIS estimates of 1997 – 2005 diabetes prevalence (age- and sex- standardized) were as follows: 5.9% for normal weight (BMI 18.5-22.9 kg/m^2) Filipinos, 3.7% for overweight (BMI 23.0-27.4 kg/m^2), and 11.3% for obese (BMI ≥ 27.5 kg/m^2) [5]. Among Filipinos with BMI ≥ 30 kg/m^2, 10.9% had diabetes [5]. Articles using other data sources estimated higher prevalence rates. In a study of men and women from five northern California Kaiser Permanente Medical Care Program centers, 21.2% had diabetes (age- and sex- adjusted) [2]. Across three publications on the NHHR project, 19.4-24.9% total diabetes prevalence was reported [41, 45, 46], with a higher prevalence (30.9%) among individuals 50 years and older [46]. Publications on the UCSD Filipino Women's Health Study reported 27.5 - 36.4% diabetes.

Korean

Two of the eight cross-sectional studies reporting on Koreans contained population-based samples (Table **5**): the California Health Interview Survey (CHIS) randomly selected 492 Korean American adults, representing 330,000 Korean American adults in California in 2003 [60], and the Hypertension Screening Project for Korean Americans in Maryland (HSP) used a stratified sampling method to include 76 Korean Americans between 1998 and 1999 [66]. The CHIS study [60] reported percent overweight (defined by 2004 WHO definitions for Asians) as 38.4% for the entire sample, 49.0% among men, and 30.7% among women. Percent obese in the total sample was 7.5%, or 10.7% of men and 5.2% of women. The Multiethnic Cohort Study in Hawaii and Los Angeles reported that percent overweight or obese (BMI ≥ 25 kg/m^2) was 31.4% for U.S.-born women and 9.4% for Korea-born women [56]. Finally, another study of Korean elderly (age 60-95, n=90) in Chicago found 6.3% obesity in men and 5.0% obesity in women, defined as BMI ≥ 30 kg/m^2 [3]. BMI for Korean men ranged from 23.3 kg/m^2 for elderly men living in Chicago to 24.9 kg/m^2 among acculturated men in California [3, 92]. Reports of mean BMI for women ranged from 22.1 kg/m^2 among Korean-born women and traditional Korean women [56, 92] to 26.3 kg/m^2 among elderly Koreans in Washington State [74].

Only two studies reported percent diabetes among Koreans in the U.S.. Among 497 Korean Americans residing in Michigan, 11% of men and 10% of women had self-reported diabetes (age-adjusted) [57]. Among elderly Koreans from Maryland, 22.7% of males and 15.4% of females had diabetes (fasting glucose ≥ 126 mg/dl) [65].

Vietnamese

Limited information was published for Vietnamese Americans (Table **6**). A population sample from the Centers for Disease Control and Prevention (CDC) Racial and Ethnic Approaches to Community Health (REACH) 2010 program was collected, surveying Vietnamese residents of Santa Clara County, CA who were 18 years of age and older. Among Vietnamese, 17.3% were overweight (BMI ≥ 25.0 and <30 kg/m^2) and 2.1% (95% CI: 1.6, 2.7) were obese (BMI ≥ 30 kg/m^2) [58]. Among Vietnamese refugees who

Table 5. Results of a Systematic Review of Mean BMI, Percent Overweight (ov)/Obese (ob), and Prevalence of Diabetes in Asians: Korean references (n=8)

Reference	City, State	Sample Size	Mean Age in Years ± SD	Mean BMI in kg/m^2 ± SD	Definition of ov, ob by BMI (kg/m^2)	Ov, ob, %	Diabetes, %
Cho 2006 [60]	CA[a]	492	48.5	***	ov: BMI 23-27.4 ob: BMI ≥ 27.5	ov: 38.38, SE 2.95 (total) ov: 49.03, SE 4.99 (men) ov: 30.69, SE 3.82 (women) ob: 7.51, SE 1.36 (total) ob: 10.67, SE 2.82 (men) ob: 5.22, SE 1.31 (women)	***
Kim KK 1993 [3]	Chicago, IL	90 (total) 30 (men) 60 (women)	72.1 (total)	23.3 ± 4.5 (men) 24.2 ± 3.6 (women)	ob: BMI>30.0	ob: 6.3 (men) ob: 5.0 (women)	***
Kim, MT 2001 [65]	Baltimore, MD	205 (total) 75 (men) 130 (women)	69.9 ± 6.5 (total) 69.2 ± 5.9 (men) 69.9 ± 6.8 (women)	24.5 ± 3.5 (total) 24.3 ± 3.8 (men) 24.6 ± 3.3 (women)	ov & ob: BMI ≥ 25[b]	ov & ob: 43.3 (total) ov & ob: 45.3 (men) ov & ob: 42.3 (women)	18.1 (total)[c] 22.7 (men)[c] 15.4 (women)[c]
Kim, MT 2000 [66]	MD	761	50.5	***	ov & ob: BMI ≥ 25[b]	ov & ob: 28	***
Park 2005 [56]	Los Angeles, CA & HI	274 (U.S.-born) 218 (Korea-born)	62.5 ± 8.4 (women, U.S.-born) 53.5 ± 6.6 (women, Korea-born)	23.6 ± 4.1 (women, U.S.-born)[d] 22.1 ± 4.2 (women, Korea-born)[d]	ov or ob: BMI≥25	ov or ob:31.4 (women, U.S.-born)[d] ov or ob: 9.4 (women, Korea-born)[d]	***
Sin 2009 [74]	WA[e]	87 (total) 49 (men) 38 (women)	78 ± 6.58 (men) 73 ± 5.39 (women)	25.4 (total) 24.6 ± 2.44 (men) 26.3 ± 4.58 (women)	***	***	***
Song 2004 [92]	CA[f]	1026 (traditional males) 211 (bicultural males) 97 (acculturated males) 1220 (traditional females) 205 (bicultural females) 71 (acculturated females)	***	24.2, SE 0.1 (traditional males) 24.4, SE 0.2 (bicultural males) 24.9, SE 4.1 (acculturated males) 22.1, SE 0.1 (traditional female) 21.6, SE 0.2 (bicultural females) 21.3, SE0.4 (acculturated females)	***	***	***
Yang 2007 [57]	MI	263 (men) 234 (women)	53.8 ± 11.2 (men) 49.0 ± 11.0 (women)	24.0 ± 0.2 (men)[g] 22.4 ± 0.2 (women)[g]	***	***	11 (men)[g, h] 10 (women)[g, h]

*** Data not included or specified
[a] Data from the California Health Interview Survey, a statewide survey representative of non-institutionalized adults 18 and older
[b] Reported as overweight in this publication
[c] Based on 1997 National Diabetes Data Group's diagnostic criteria of fasting glucose ≥ 126 mg/dl
[d] Adjusted for age and education
[e] King County, Snohomish County, and Pierce County, WA
[f] Representative sample of Korean adults living in CA with telephones and Korean surnames
[g] Adjusted for age
[h] Based on self-report

Table 6. Results of a Systematic Review of Mean BMI, Percent Overweight (ov)/Obese (ob), and Prevalence of Diabetes in Asians: Vietnamese References (n=3)

Reference	City, State	Sample Size	Mean Age in Years ± SD	Mean BMI in kg/m^2 ± SD	Definition of ov, ob by BMI (kg/m^2)	Ov, ob, %	Diabetes, %
Barnes 2004 [62]	TX	114[a]	***	***	ov & ob: BMI ≥ 25[b]	ov & ob: 12.3	***
Nguyen 2009 [58]		4254[c]	18-34 years = 26.7%, 95% CI: 25.1, 28.3 35-54 years = 43.8% 95% CI: 42.2, 45.4 55+ years = 29.5% 95% CI: 28.0, 30.9	***	ov: 25.0 ≤ BMI < 30 ob: BMI ≥ 30	ov: 17.3, 95% CI: 16.0, 18.7[d] ob: 2.1, 95% CI: 1.6, 2.7[d]	5.3, 95% CI: 4.7, 6.0[d,e]
Sorkin 2008 [93]	CA	359[f]	64.6	***	***	***	15.6[e,g]

*** Data not included or specified
[a] Population-based survey of refugees in a city in TX
[b] Reported as overweight in publication
[c] From the CDC Racial and Ethnic Approaches to Community Health 2010 program
[d] Age-standardized
[e] Based on self-report
[f] Data from the California Health Interview Survey, a statewide survey representative of non-institutionalized adults 18 and older
[g] Adjusted for age, sex, and education

- The purpose of this review was to describe the state of overweight, obesity, and diabetes in specific Asian American groups using peer-reviewed publications from 1988 - 2009.
- Data were only identified for Asian Indians, Chinese, Filipinos, Koreans, South Asians, and Vietnamese. No published reports were found for other studied Asian subgroups.
- Asian American subgroups are heterogeneous in the prevalence of overweight, obesity, and diabetes.
- Available studies on Asian American subgroups are not representative, limiting comparisons between the different subgroups.
- Available studies do not provide enough consistent information to create summary estimates for any one Asian American subgroup.
- Despite a generally held belief that all Asian Americans experience unique risk profiles for obesity, diabetes, and other diseases, inadequate data for various Asian America subgroups actually exists.
- Future research must adopt standardized approaches and provide representative estimates of specific Asian American subgroups to adequately understand and improve health among Asian Americans.

Fig. (4). Key Messages.

arrived to one Texas city and were screened, 12.3% were overweight (BMI ≥25 kg/m^2) [62]. Mean BMI was not reported. Two publications reported percent self-reported diabetes, ranging from 5.3% (age-standardized) to 15.6% (adjusted for age, sex, and education) [58, 93].

DISCUSSION

The purpose of this review was to systematically describe the state of overweight, obesity, and diabetes in specific Asian American subgroups. Our findings and key discussion points are summarized in (Fig. **4**). Contrary to common approaches that generalize across Asians, the results of this review suggest that Asian American subgroups are vastly heterogeneous for these conditions, and generalizing them into one "Asian" group may be inappropriate. Also, despite the high volume of published reports on these conditions, this review reveals that representative studies are sorely lacking, exposing the inability to create summary estimates for specific Asian America subgroups, thereby prohibiting between-group comparisons of disease prevalence and risk factor associations. Among reported estimates for men and women, prevalence of overweight varied from 12.8 – 46.7% in Asian Indians, 15.0 – 38.2% in Chinese, and 15.0 – 46.5% in Filipinos; similarly, reports of obesity varied from 5.0 – 49.8% in Asian Indians, 2.4 – 47.0% in Chinese, and 8.6 –

59.0% in Filipinos. Only one or no estimate was provided for men and women in the other Asian subgroups. Reported prevalence of diabetes in samples of men and women ranged from 3.9 – 32.9% in Asian Indians, 1.0 - 11.3% in the South Asian category, 2.2 - 28% in Chinese, 3.7 – 30.9% in Filipinos, and 5.3 - 15.6% in Vietnamese, with one estimate for Koreans (18.1%).

A major finding of this review was that most studies about Asian American subgroups utilize designs that prohibit between-subgroup and within-subgroup comparisons. Many of the studies drew convenience samples from specific geographic regions, defined unique inclusion/exclusion criteria, and employed different definitions of overweight, obesity, and diabetes, limiting generalizability of data. In addition, studies did not always provide measures of overweight and obesity alongside measures of diabetes, making it difficult to study the relationship between overweight and diabetes. Approximately half of all articles were from seven studies: MESA, SWAN, Filipino Women's Health Study, HHR, BRFS in Guam, Rancho Bernardo Study, and NHIS, of which only NHIS was nationally representative. For the 20% of all studies that accounted for confounding factors (i.e., age, sex) in their estimates, differing approaches were employed (e.g., age adjustment using study sample versus age-standardization to external population), also impacting comparability. Ultimately, these results provide conclusive evidence that standardized approaches to surveying Asian American subgroups are needed.

This systematic review has several limitations. All studies defined individuals based on country of origin rather than by genotypes of ethnicity, which could also play a role in prevalence differences. Additionally, the review covers a 20-year period that coincides with the rapid increases in the overall BMI among U.S. adults, making it difficult to distinguish overweight associated with ethnicity compared to overweight associated with the time period. Another limitation of this review is the inability to account for immigration and generation. First or second generation immigrants experience different obesity and disease rates compared to their ancestors [94]. Immigrants tend to have lower BMI upon migration, and foreign-born Asian Americans are significantly less overweight and obese than U.S.-born Asian Americans, though increased duration of residence in the U.S. is correlated with increased obesity [95-98]. Studies of Asian Americans by immigrant generational status also have observed a trend of increasing obesity and diabetes with later generations [99]. For example, the prevalence of diabetes is approximately 4 times higher among second-generation Japanese-Americans than among native Japanese [100].

Despite these limitations, the strengths of this review include the rigorous search for publications, which was systematic and thorough. With professional consultation in biomedical database searching and management from an experienced university librarian, the results of the PubMed search and the hand searches identified those publications which the authors expected to find based on their expertise in chronic disease epidemiology, medicine, and Asian American culture, attitudes, and beliefs. The searches also identified additional publications relevant to the review topic. In addition to the rigorous search, another strength is that the Asian American population is particularly well-suited to study differences in the relationship between overweight, obesity, and diabetes because the relationship in this population seems to be unique and may assist in unveiling underlying mechanisms of these health conditions [101]. Historically, data presenting the prevalence of diabetes, overweight, and obesity among Asian American populations have included them as a one collective group, but more recently, literature has emerged showing variations in diabetes and obesity risk when comparing specific Asian American subgroups to whites or blacks. Since 1960, the U.S. Asian population has increased almost fivefold, with more than 14 million Asians in the U.S. in 2009 and accounting for nearly 28% of the nation's foreign-born population [102]. Continued research on the heterogeneity in diabetes occurrence and risks among Asian Americans is necessary considering that this population is projected to comprise 9% of the total U.S. population by 2050 [103] and that the number of people living with diabetes is projected to increase from 366 million in 2011 to 552 million by 2030 [104]. It is of critical importance to study the relationship between ethnicity and chronic disease now, before extensive intermarriages between Asians and non-Asians makes it more difficult to identify and recruit specific Asian subgroups for studies.

Given the rapid recent and projected growth of the Asian American population, national surveys can improve surveillance and monitoring of this group through integration into existing systems [105] (i.e., BRFS, NHIS, NHANES) and through oversampling of Asian American subgroups. Improved surveillance would enhance national data and could be used to establish better prevalence estimates across Asian subgroups in the U.S. [106]. This includes Japanese Americans, a subgroup that was excluded from this study because Japanese migration to the U.S. occurred before the 20-year period of interest and Japanese Americans (1^{st}, 2^{nd}, and 3^{rd} generation) have been extensively studied previously, unlike the Asian subgroups included in this review. In addition, large-scale population based analyses addressing more complex disease determinants of obesity and diabetes (beyond single gene polymorphisms) might improve the understanding of the relative impact of genetic and environmental factors linking them. Identifying the key risk factors and pathophysiolgical mechanisms that lead to disease is essential to understanding the etiology of the disease and for the development of sound policies, including prevention and treatment strategies, for improved health among Asians.

In summary, this review summarized and synthesized data published in the past 20 years on the prevalence of diabetes, overweight, and obesity among Asian American subpopulations in the U.S. Although this review showed there are differences across Asian American subgroups, quantifying these differences is challenging because of the lack of nationally representative, standardized data *within* the Asian American group, a large and growing population. Future efforts to estimate levels of overweight, obesity, and diabetes must standardize approaches and include specific subgroups of Asian Americans to better understand and improve the health of these minorities in the United States.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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Chapter 4: Dissertation Methods

The research presented in this dissertation draws upon a secondary analysis of an existing trial to examine pathophysiological factors of diabetes. This trial, the Diabetes Community Lifestyle Improvement Program (D-CLIP) trial was originally designed to assess changes in the incidence of diabetes between lifestyle intervention group and control. The trial is being conducted in Chennai (formerly Madras), India's fourth largest city and the largest city in Southern India. Study classes and testing take place at Dr. Mohan's Diabetes Specialities Centre/Madras Diabetes Research Foundation (MDRF). This project is supported by a BRiDGES Grant from the International Diabetes Federation. BRiDGES, an International Diabetes Federation project, is supported by an educational grant from Eli Lilly and Company. Methods pertaining to the secondary analysis of the data in D-CLIP are presented in the following sections.

Study Participants

This dissertation draws upon a sample of men and women from Chennai, India involved in the Diabetes Community Lifestyle Improvement Program (D-CLIP), a primary prevention trial testing the effects of a step-wise model of diabetes prevention, including a culturally tailored, intensive lifestyle intervention, plus metformin when needed (14). Participants were recruited using community-wide approaches at large-scale community events, housing/apartment complexes, local businesses, places of worship and educational institutions; through clinic records at the study site; and through direct referral by health care providers at the clinic. Community-based screening (n = 19,377) included a short survey, anthropometric measurements and a random capillary

blood glucose test using a glucose meter (Lifescan, Johnson & Johnson, Milpitas, California, USA). Community-based screening was used to identify individuals for enrollment in the randomized control trial. Individuals who were pregnant, breastfeeding, with a history or evidence of heart disease, or with any other serious illness were excluded from the study. Screened volunteers who were 20 – 65 years of age; with a random capillary blood glucose of greater than or equal to 6.1 mmol/l (110 mg/dl); and without known type 2 diabetes were eligible for clinic-based screening (D-CLIP baseline testing), which included a 75g OGTT performed after an overnight fast in the morning.

Among all subjects meeting the eligibility criteria described above, 1,285 were eligible for clinic-based screening and provided informed consent (Figure 4-1). These participants formed the study sample for Aims 1 and 2 of this dissertation (**Chapters 5** and **6**). Next, those with high risk for developing diabetes (baseline fasting plasma glucose indicating IFG: 100–125 mg/dL and/or 2-hour post-load glucose indicating IGT: 140–199 mg/dL) and those who were also overweight (based on South Asian-appropriate cut-points (12) as BMI ≥23 kg/m2 and/or a waist circumference ≥90 cm for men and ≥80 cm for women) were eligible for randomization into the trial. Among 599 individuals who were randomized to the intervention arm or to the standard of care control arm between 2008 and 2011, individuals who returned for a one-year follow up by December 2012 were eligible for longitudinal analyses for this research (Figure 4-1). These participants formed the study sample for Aim 3 of this dissertation (n=491, **Chapter 7**).

Across all analyses (**Chapters 5, 6,** and **7**), subjects were excluded for missing glucose or insulin measures of the OGTT at any time point (i.e., 0 or 30 or 120 minutes) or for having negative or zero values of the insulinogenic index (IGI), a measure of the

early insulin response in the OGTT (41), calculated as the ratio of change in insulin to the change in glucose from 0 to 30 minutes (i.e., $\Delta I_{0\text{-}30}/\Delta G_{0\text{-}30}$). Only individuals with a positive numerator and positive denominator for IGI were included in analyses. Figure 4-1 is a flow diagram of participant recruitment, exclusions, and number of individuals eligible for analyses in Aims 1-3 of this dissertation. Figure 4-2 provides the timeline for data collection. The study was approved by the Emory University Institutional Review Board and the Madras Diabetes Research Foundation Ethics Committee.

Figure 4-1. Flow diagram of study sample and exclusions across Dissertation Aims 1, 2, and 3

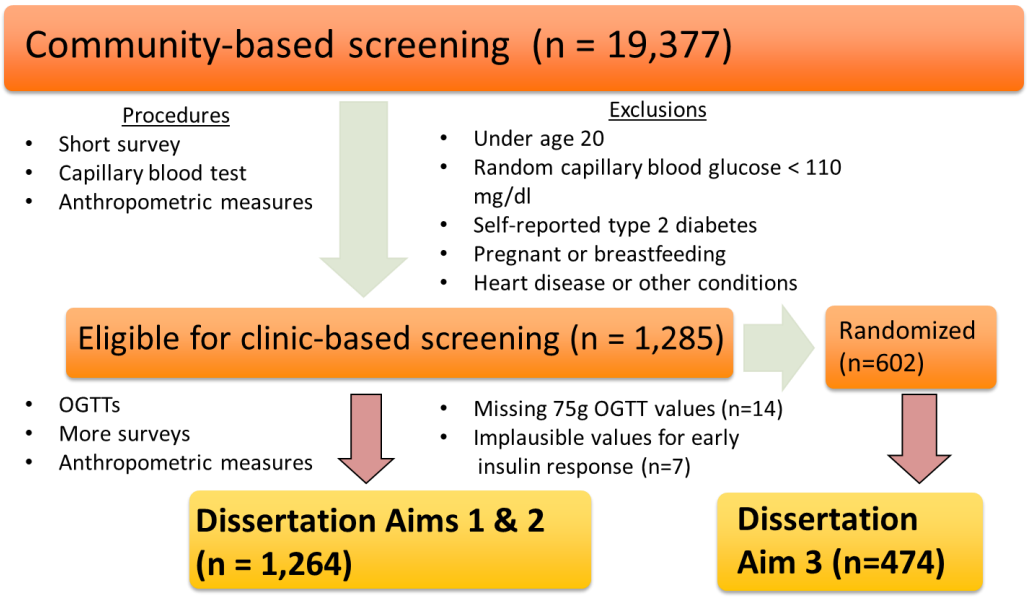
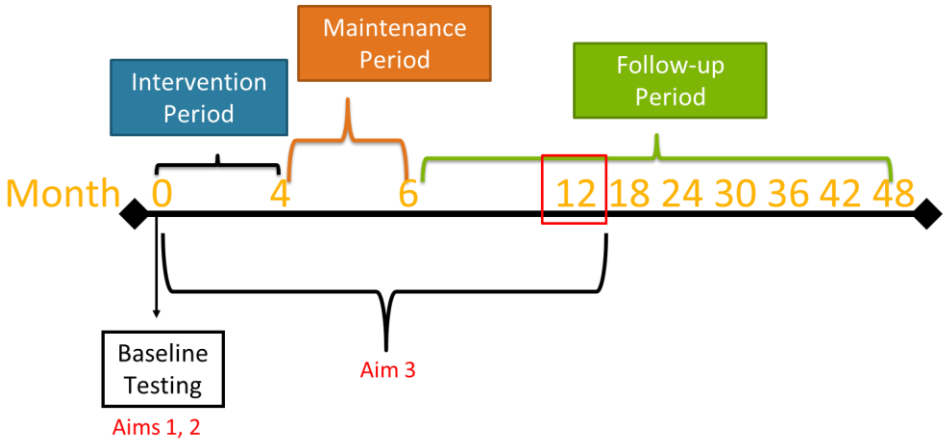


Figure 4-2. D-CLIP timeline and time periods for Dissertation Aims 1, 2, and 3



Study Procedures

The demographic, anthropometric and glucose tolerance data collected are described here, with additional details provided elsewhere (14). After an 8-hour overnight fast, subjects participated in a standard 75-g oral OGTT (83) with plasma glucose and insulin sampled at 0, 30 and 120 minutes. All OGTTs were performed in the morning, which controlled for diurnal patterns of insulin secretion and insulin action. Other collected data included body weight, height, waist circumference and family history of diabetes, defined as having one or more first degree relatives with type 2 diabetes. For body weight assessment, subjects were asked to wear light clothing, and weight was recorded after shoes and heavy jewelry were removed. Height was measured with a stadiometer to the nearest cm with subjects standing upright without shoes. BMI was calculated as mass (kg) / height squared (m^2). Waist circumference was measured twice at the smallest horizontal girth between the costal margins and the iliac crests at minimal respiration using a non-elastic measuring tape and averaged. OGTT samples

were collected in EDTA, separated and stored at -80^{o}C. Plasma glucose (hexokinase method) was measured on a Hitachi 912 Autoanalyzer (Hitachi, Mannheim, Germany) using kits supplied by Roche Diagnostics (Mannheim, Germany). Insulin concentrations were estimated using an electrochemiluminescence method (COBAS E 411, Roche Diagnostics, Mannheim, Germany). The intra- and inter- assay coefficient of variation for the biochemical assays ranged between 3.1 to 7.6 per cent. Samples were processed in a laboratory accredited nationally by the National Accreditation Board for Testing and Calibration Laboratories and internationally by the College of American Pathologists.

Key Variables

Measures of glycemia were fasting plasma glucose (mmol/L), 2-hr glucose (mmol/L), and HbA1c (%). Glycemia included normoglycemia, prediabetes, and diabetes (8). Diabetes was defined as HbA1C $\geq$ 6.5%; fasting plasma glucose $\geq$ 7.0 mmol/L (126 mg/dL); or 2-hour postchallenge glucose $\geq$ 11.1 mmol/L (200 mg/dL). Prediabetes was defined as HbA1c 5.7 – 6.4%; fasting plasma glucose 5.6 mmol/L (100 mg/dL) to 6.9 mmol/L (125 mg/dL); or 2-hour postchallenge glucose between 7.8 mmol/L (140 mg/dL) and 11.0 mmol/L (199 mg/dL). Beta-cell function was measured using the oral disposition index, denoted as DI_o, calculated as IGI adjusted for insulin sensitivity: $DI_o = ([\Delta I_{0-30} / \Delta G_{0-30}] \times [1/\text{fasting insulin}])$ (41). Insulin resistance was estimated using HOMA (HOMA-IR = [fasting insulin mU/L x fasting glucose, mmol/L] / 22.5) (84). Covariates included age, BMI, waist circumference, and family history of disease.

Data Analysis

Analyses were performed using SAS 9.3 (SAS Institute, Cary, NC). Continuous variables were tested for normality, and non-normally distributed variables were log-transformed as required to meet assumptions of regression. T-tests were used for continuous variables, and chi-square tests and Analysis of Variance were used for categorical variables. Modeling techniques included polytomous logistic regression, linear regression, and piecewise linear spline regression. Interaction effects were tested; all interaction terms were modeled, and backward elimination was used to remove insignificant interaction terms, one at a time. Following interaction testing, confounding was assessed by comparing the gold standard model (i.e., the model with all significant interaction terms and all potential confounders) with alternate models that contained fewer potential confounders. A variety of alternate models were created to contain all possible combinations of confounders. Alternate models which contained parameter estimates of DI_o within 10% of the gold standard model and which had the smallest standard error around the parameter estimate were selected as final models after the confounding assessments.

Chapter 5: Evidence of Reduced Beta-Cell Function in Asian Indians with Mild Dysglycemia

The following 7 pages:

Evidence of Reduced Beta Cell Function in Asian Indians With Mild Dysglycemia

Lisa R. Staimez, mph[1]
Mary Beth Weber, phd, mph[2]
Harish Ranjani, phd, cde[3]
Mohammed K. Ali, mbchb, msc[1,2]
Justin B. Echouffo-Tcheugui, md, phd[2]
Lawrence S. Phillips, md[4,5]
Viswanathan Mohan, md, frcp, phd, dsc[3]
K.M. Venkat Narayan, md, msc, mba[1,2,6]

OBJECTIVE—To examine β-cell function across a spectrum of glycemia among Asian Indians, a population experiencing type 2 diabetes development at young ages despite low BMI.

RESEARCH DESIGN AND METHODS—One-thousand two-hundred sixty-four individuals without known diabetes in the Diabetes Community Lifestyle Improvement Program in Chennai, India, had a 75-g oral glucose tolerance test, with glucose and insulin measured at 0, 30, and 120 min. Type 2 diabetes, isolated impaired fasting glucose (iIFG), isolated impaired glucose tolerance (iIGT), combined impaired fasting glucose and impaired glucose tolerance, and normal glucose tolerance (NGT) were defined by American Diabetes Association guidelines. Measures included insulin resistance and sensitivity (homeostasis model assessment of insulin resistance [HOMA-IR], modified Matsuda Index, 1/fasting insulin) and β-cell function (oral disposition index = [Δinsulin$_{0-30}$/Δglucose$_{0-30}$] × [1/fasting insulin]).

RESULTS—Mean age was 44.2 years (SD, 9.3) and BMI 27.4 kg/m^2 (SD, 3.8); 341 individuals had NGT, 672 had iIFG, IGT, or IFG plus IGT, and 251 had diabetes. Patterns of insulin resistance or sensitivity were similar across glycemic categories. With mild dysglycemia, the absolute differences in age- and sex-adjusted oral disposition index (NGT vs. iIFG, 38%; NGT vs. iIGT, 32%) were greater than the differences in HOMA-IR (NGT vs. iIFG, 25%; NGT vs. iIGT, 23%; each $P < 0.0001$). Compared with NGT and adjusted for age, sex, BMI, waist circumference, and family history, the odds of mild dysglycemia were more significant per SD of oral disposition index (iIFG: odds ratio [OR], 0.36; 95% CI, 0.23–0.55; iIGT: OR, 0.37; 95% CI, 0.24–0.56) than per SD of HOMA-IR (iIFG: OR, 1.69; 95% CI, 1.23–2.33; iIGT: OR, 1.53; 95% CI, 1.11–2.11).

CONCLUSIONS—Asian Indians with mild dysglycemia have reduced β-cell function, regardless of age, adiposity, insulin sensitivity, or family history. Strategies in diabetes prevention should minimize loss of β-cell function.

Type 2 diabetes mellitus is a global problem, with 80% of all cases worldwide occurring in low- and middle-income countries (1). However, despite the increasing prevalence of type 2 diabetes, the etiology of the disease remains incompletely understood. Previously invoked as the driving feature of diabetes, increased insulin resistance can trigger increased insulin production to maintain normoglycemia and, over time, can strain β cells to the point at which insulin production is no longer adequate (2–4), i.e., β-cell "exhaustion." Characteristics associated with insulin resistance, particularly older age, obesity, and physical inactivity, are strong risk factors for diabetes (5).

Yet, poor β-cell function also may have more of a primary role in diabetes development. The inadequate β-cell response to physiologic needs for insulin not only may be an acquired feature (e.g., as a result of insulin resistance) but also, at least in some individuals, may be an inherent feature. β-cell dysfunction has been detected early in the pathogenesis of the disease (6), with recent cross-sectional and longitudinal studies detecting dysfunction in people with prediabetes or even normoglycemia (7–10). Supported by recent genetic discoveries (11), these studies suggest that some individuals have an underlying susceptibility to poor β-cell function (12) and that β-cell dysfunction may be an early driving metabolic feature of diabetes development.

Most studies of diabetes pathogenesis have been conducted in populations of European descent; however, more people have diabetes in other populations worldwide. Asian Indians, in particular, experience high rates of type 2 diabetes (13) at younger ages and lower BMI values (14) compared with other populations. They have high basal insulin levels (15) that are not entirely explained by obesity or adverse fat distribution (16), which are commonly cited factors related to insulin resistance. Considering these characteristics, Asian Indians may be an ideal population to utilize for developing a better understanding of the relative roles of β-cell function and insulin resistance in the pathogenesis of type 2 diabetes. Previous studies that have examined the etiology of diabetes in Asian Indians have produced conflicting findings. Altered β-cell function has been associated with impaired glucose tolerance (IGT) (17), has not been associated with IGT (18,19), and has been associated with impaired fasting glucose (IFG) but not IGT (20). Furthermore, β-cell function has not always been evaluated rigorously in Asian Indians (i.e., expressed relative to the insulin resistance of each individual) (21). We investigated the associations between the pathophysiologic mechanisms of insulin resistance and β-cell function with glycemic status in a large cohort (n = 1,264) of Asian Indians in Chennai, India.

From the [1]Nutrition and Health Sciences Program, Graduate Division of Biomedical and Biological Sciences, Laney Graduate School, Emory University, Atlanta, Georgia; the [2]Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, Georgia; the [3]Madras Diabetes Research Foundation, Global Diabetes Research Center, WHO Collaborating Centre for Noncommunicable Diseases Prevention and Control and International Diabetes Federation Centre of Education, Chennai, India; the [4]Division of Endocrinology, Department of Medicine, School of Medicine, Emory University, Atlanta, Georgia; the [5]Veterans Affairs Medical Center, Decatur, Georgia; and the [6]Department of Medicine, School of Medicine, Emory University, Atlanta, Georgia.
Corresponding author: Lisa R. Staimez, lisa.staimez@emory.edu.
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RESEARCH DESIGN AND METHODS

Study population

Study subjects were individuals in the Diabetes Community Lifestyle Improvement Program, a primary prevention trial in Chennai (formerly Madras) testing the effects of a stepwise model of diabetes prevention, including a culturally tailored and intensive lifestyle intervention plus metformin when needed (22). Community-wide recruitment targeted men and women at large-scale community events, housing or apartment complexes, local businesses, places of worship, and educational institutions, through clinic records at the study site, and through direct referral by health care providers at the clinic. Community-based screening (n = 19,377) included a short survey, anthropometric measurements, and random capillary blood glucose test using a glucose meter (Lifescan; Johnson & Johnson, Milpitas, CA). Screened volunteers who were 20–65 years old with a random capillary blood glucose of ≥6.1 mmol/L (110 mg/dL) and without known type 2 diabetes were eligible for clinic-based screening (Diabetes Community Lifestyle Improvement Program baseline testing), which included a 75-g oral glucose tolerance test (OGTT) performed after an overnight fast.

Individuals who were pregnant, breastfeeding, with a history or evidence of heart disease, or with any other serious illness were excluded from the study. All subjects provided informed consent and participated in clinic-based screening between 2008 and 2011. Among the 1,285 individuals tested in clinic-based screening, 14 participants were excluded for missing glucose or insulin measures of the OGTT at any time point (i.e., 0, 30, or 120 min). An additional seven individuals were excluded for having negative or zero values of the insulinogenic index (IGI), a measure of the early insulin response in the OGTT (23), calculated as the ratio of change in insulin to the change in glucose from 0 to 30 min (i.e., $\Delta I_{0–30}/\Delta G_{0–30}$). The final number of participants included in the present analyses was 1,264. The study was approved by the Emory University Institutional Review Board and the Madras Diabetes Research Foundation Ethics Committee.

Study procedures

Diabetes Community Lifestyle Improvement Program baseline testing included the collection of demographic, anthropometric, and glucose tolerance data (22). After fasting overnight for at least 8 h, subjects participated in a standard 75-g oral OGTT (24), with plasma glucose and insulin sampled at 0, 30, and 120 min. Other collected data included demographics, body weight, height, waist circumference, and family history of diabetes (defined as having one or more first-degree relatives with type 2 diabetes). For body weight assessment, subjects were asked to wear light clothing and weight was recorded after shoes and heavy jewelry were removed. Height was measured with a stadiometer to the nearest centimeter with subjects standing upright without shoes. BMI was calculated as mass (kg) divided by height squared (m^2). Waist circumference was measured twice at the smallest horizontal girth between the costal margins and the iliac crests were measured at minimal respiration using a nonelastic measuring tape and averaged. OGTT samples were collected in EDTA, separated, and stored at −80°C. Plasma glucose (hexokinase method) was measured on a Hitachi 912 Autoanalyzer (Hitachi, Mannheim, Germany) using kits supplied by Roche Diagnostics (Mannheim, Germany). Insulin concentrations were estimated using an electrochemiluminescence method (COBAS E 411; Roche Diagnostics, Mannheim, Germany). The intra-assay and interassay coefficients of variation for the biochemical assays ranged between 3.1 and 7.6%. Samples were processed in a laboratory accredited nationally by the National Accreditation Board for Testing and Calibration Laboratories and internationally by the College of American Pathologists.

Key variables

The glycemic status outcomes for this study were defined by the following American Diabetes Association criteria (25): diabetes as fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) or 2-h postload glucose ≥11.1 mmol/L (200 mg/dL), or both; isolated IFG (iIFG) as fasting plasma glucose 5.6–6.9 mmol/L (100–125 mg/dL) and 2-h postload glucose <7.8 mmol/L (140 mg/dL); isolated IGT (iIGT) as 2-h postload glucose 7.8–11.0 mmol/L (140–199 mg/dL) and fasting plasma glucose <5.6 mmol/L (100 mg/dL); NGT as fasting plasma glucose <5.6 mmol/L (100 mg/dL) and 2-h postload glucose <7.8 mmol/L (140 mg/dL); and combined IFG and IGT (IFG plus IGT) as fasting plasma glucose 5.6–6.9 mmol/L (100–125 mg/dL) and 2-h postload glucose 7.8–11.0 mmol/L (140–199 mg/dL). Prediabetes was defined as iIFG, iIGT, or IFG and IGT. Mild dysglycemia was defined as iIFG or iIGT.

The primary measure for β-cell function was the oral disposition index, denoted as DI_o, calculated as follows as IGI adjusted for insulin sensitivity: $DI_o = ([\Delta I_{0–30}/\Delta G_{0–30}] \times [1/\text{fasting insulin}])$ (23). Insulin resistance was estimated using homeostasis model assessment of insulin resistance (HOMA-IR; [fasting insulin × fasting glucose]/22.5) (26). The modified Matsuda Index for whole-body insulin sensitivity was calculated as follows: (10,000/square root of [fasting glucose × fasting insulin] × [mean glucose × mean insulin]), with mean glucose and mean insulin each calculated from values at 0, 30, and 120 min of the OGTT (27,28). Total area under the curve (AUC) for insulin and AUC for glucose were calculated using the trapezoidal rule, and a ratio of the two was created ($AUC_{ins/glu}$). Secondary measures of β-cell function included the following: $([\Delta I_{0–30}/\Delta G_{0–30}] \times [1/\text{HOMA-IR}])$; $([\Delta I_{0–30}/\Delta G_{0–30}] \times [\text{modified Matsuda Index}])$; $AUC_{insulin/glucose} \times (1/\text{fasting insulin})$; $AUC_{insulin/glucose} \times (1/\text{HOMA-IR})$; and $AUC_{insulin/glucose} \times (\text{modified Matsuda Index})$. Other covariates included BMI and waist circumference. Categories of overweight/obesity were those defined by the World Health Organization (29) both generically (25.0≤BMI<30.0 kg/m^2 for overweight; BMI ≥30.0 kg/m^2 for obesity) and specifically for Asian populations (23.0<BMI≤27.4 kg/m^2 for overweight; BMI ≥27.5 kg/m^2 for obesity). Waist circumference was categorized dichotomously, using waist ≥90 cm for men and ≥80 cm for women (30), and by using tertiles.

Statistical analysis

Analyses were performed using SAS 9.3 (SAS Institute, Cary, NC). ANOVA allowed comparison of DI_o across glycemic status categories, including the Tukey test for multiple comparisons. Non-normally distributed variables were log-transformed as required to meet assumptions of regression. A Score test was conducted to evaluate the possible use of ordinal logistic regression; the proportional odds could not be assumed as required (i.e., the null hypothesis that the model was constrained by the proportional odds assumption was rejected [χ^2 = 98.59; degrees of freedom = 3; $P < 0.0001$]).

Table 1—*Characteristics of participants in the Diabetes Community Lifestyle Improvement Program subdivided by glycemic status*

Characteristic	Total N = 1,264	NGT n = 341	iIFG n = 200	iIGT n = 202	IFG plus IGT n = 270	Diabetes n = 251
Male, n (%)	803 (63.5)	209 (61.3)	118 (59.0)	133 (65.8)	168 (62.2)	175 (69.7)
Age, years	44.21	9.27	41.99	9.03	44.69	9.33	43.13	9.22	45.30	9.27	46.54	8.89
BMI, kg/m^2	27.41	3.76	26.77	3.62	27.44	3.79	27.43	3.35	28.26	4.16	27.34	3.65
Waist circumference, cm	93.98	9.40	92.21	9.30	93.09	9.63	94.25	8.88	95.75	9.34	94.98	9.39
Fasting glucose, mmol/L	5.80	0.95	5.07	0.29	5.87	0.30	5.13	0.27	6.03	0.36	7.03	1.22
30-min glucose, mmol/L	9.81	1.88	8.41	1.21	9.88	1.31	9.05	1.15	10.12	1.31	11.95	1.96
2-h glucose, mmol/L	8.81	3.05	6.24	0.91	6.61	0.89	8.74	0.79	9.27	0.97	13.64	2.70
Fasting insulin, pmol/L	77.44	45.80	65.17	45.20	70.26	35.04	79.35	38.96	85.48	54.08	89.66	44.77
30-min insulin, pmol/L	504.83	343.78	594.59	363.96	532.53	354.34	636.40	407.96	433.96	268.41	331.14	210.55
2-h insulin, pmol/L	784.44	570.28	615.40	447.49	615.07	426.08	1,145.99	725.91	871.88	538.24	764.02	560.86
1/fasting insulin, L/pmol	0.017	0.009	0.020	0.010	0.017	0.008	0.016	0.009	0.015	0.009	0.014	0.009
Insulinogenic index, IGI ($pmol_{ins}/mmol_{glu}$)	124.23	156.43	188.20	252.44	127.32	108.48	148.35	104.13	89.91	64.52	52.37	43.37
HOMA-IR [$mmol_{glu} \times pmol_{ins}/(L^2)$]	20.22	12.84	14.72	10.22	18.36	9.26	18.17	9.13	22.88	14.05	27.96	15.07
Modified Matsuda [$(L^2)/mmol_{glu} \times pmol_{ins}$]	10.52	6.20	13.59	7.16	11.27	5.68	9.39	5.16	9.11	4.99	8.17	5.35
Oral disposition index ($L/mmol_{glu}$)*	1.30	2.35	2.49	2.05	1.56	1.90	1.69	1.75	0.99	1.86	0.51	1.86
IGI × (1/HOMA-IR) ($L/mmol_{glu}$)^2*	5.11	2.60	11.08	2.07	5.97	1.94	7.43	1.77	3.70	1.89	1.65	2.02
IGI × mod Matsuda ($L/mmol_{glu}$)^2*	804.92	2.35	1,702.50	1.94	1,000.63	1.80	988.64	1.60	594.21	1.72	287.34	1.77
$AUC_{ins/glu}$ × 1/fasting insulin*	0.77	1.76	1.10	1.50	0.81	1.50	1.04	1.52	0.67	1.46	0.40	1.66
$AUC_{ins/glu}$ × 1/HOMA-IR*	3.00	1.97	4.90	1.53	3.12	1.54	4.57	1.55	2.52	1.49	1.29	1.88
$AUC_{ins/glu}$ × modified Matsuda*	473.50	1.69	752.12	1.30	522.73	1.29	608.33	1.28	404.96	1.28	225.70	1.55

Data are mean and SD unless otherwise stated. *Geometric mean and geometric SD provided for DI_o and secondary measures of beta-cell function.

Therefore, polytomous logistic regression, rather than ordinal logistic regression, was determined appropriate, and we assessed associations of glycemic status with each continuous independent variable (per SD change).

Interaction effects of DI_o and covariates (sex, age, BMI, and waist circumference) on DI_o were tested by fitting interaction terms in the models (including all other covariates) and using hierarchical backward elimination to remove interaction terms that were insignificant at the $P < 0.05$ level. Age, BMI, and waist circumference were fitted as continuous and categorical variables. The hyperbolic relationship of insulin secretion and insulin sensitivity (21) was assessed using linear regression to estimate $\ln(\Delta I_{0–30} / \Delta G_{0–30})$ or $\ln(AUC_{insulin/glucose})$ as a function of ln(1/fasting insulin) or ln (1/HOMA-IR) or ln(modified Matsuda Index). A hyperbolic relationship was confirmed if the slope was approximately equal to −1 and 95% CI excluded 0 (23,31). Data were expressed as mean and SD.

RESULTS—Table 1 provides baseline characteristics for the participants across glycemic status groups. Among all participants, the mean age was 44.2 years (9.3), and 37% were female. According to specific World Health Organization cut-offs for Asians, 47% were overweight and 45% were obese. According to generic BMI cut-points, 52% were overweight and 21% were obese. Mean waist circumference among men and women was 97.1 cm (SD, 8.5) and 88.6 cm (SD, 8.5), respectively. One-fifth had newly diagnosed diabetes (19.9%), more than half (53.2%) had prediabetes (15.8% with iIFG; 16.0% with iIGT; and 21.4% with IFG plus IGT), and 31.9% had mild dysglycemia (15.8% iIFG and 16.0% iIGT).

Using our primary measure for β-cell function, DI_o, the unadjusted mean (L/mmol) was highest in NGT and lowest among those with more severe disease (IFG plus IGT and diabetes): NGT, 2.49; iIFG, 1.56; iIGT, 1.69; IFG plus IGT, 0.99; and diabetes, 0.51. HOMA-IR, fasting insulin, and 1/modified Matsuda index were all lowest in NGT and all highest in diabetes. DI_o was significantly different ($P < 0.05$) for every pair-wise comparison of glycemic status groups except iIFG and iIGT. There was a steep difference in mean DI_o between NGT and iIFG (−38%) and NGT and iIGT (−32%; both $P < 0.0001$). Like DI_o, HOMA-IR was significantly different between every pair-wise comparison of glycemic status groups

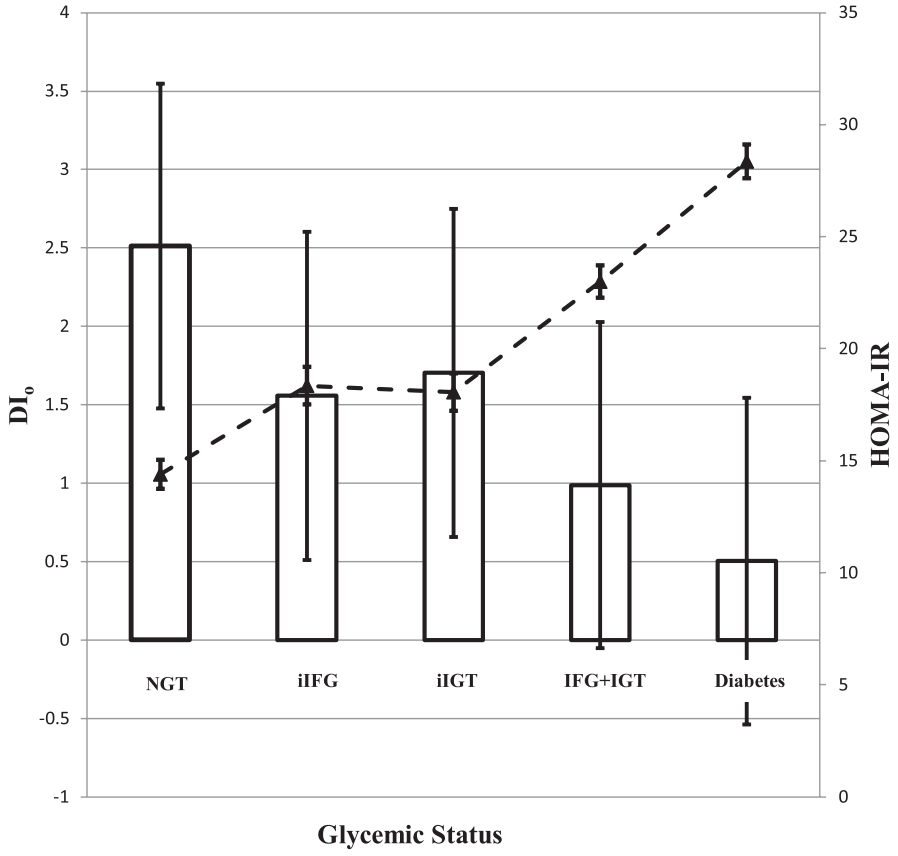

Figure 1—*Age- and sex-adjusted mean oral disposition index and mean HOMA-IR across glycemic status. White bars indicate DI$_o$; filled triangles (▲) indicate HOMA-IR. Error bars indicate SE estimates. Geometric means and geometric SE were calculated for DI$_o$ (L/mmol). HOMA-IR is presented as ($mmol_{glu} \times mmol_{ins}$)/$L^2$).*

except iIFG and iIGT. Compared with NGT, HOMA-IR was 25% greater in iIFG and 23% greater in iIGT (both $P < 0.0001$). However, unlike HOMA-IR, the modified Matsuda Index was significantly different between every pair-wise comparison of glycemic status groups except between iIGT and IFG plus IGT, iIGT and diabetes, and IFG plus IGT and diabetes. Differences between glycemic status levels remained after adjustment for age and sex (Fig. 1). Furthermore, differences in mean DI$_o$ persisted after adjustment for age, sex, BMI, waist circumference, and family history as follows: DI$_o$ was 2.48 L/mmol in NGT vs. 1.55, 1.69, 1.00, and 0.50 L/mmol in iIFG, iIGT, IFG plus IGT, and diabetes, respectively (all $P < 0.0001$ vs. NGT). Across the same glycemic categories, HOMA-IR ($mmol_{glu} \times pmol_{ins}/L^2$) was 15.29, 18.52, 18.02, 21.98, and 28.18 (all $P < 0.05$ vs. NGT) and the modified Matsuda Index [$(L^2)/mmol_{glu} \times pmol_{ins}$] was 13.31, 11.14, 9.49, 9.55, and 8.09 (all $P < 0.0001$ vs. NGT), and all were adjusted for age, sex, BMI, waist circumference, and family history.

A hyperbolic relationship was found between insulin sensitivity and insulin secretion. Using linear regression to estimate ln(IGI) as a function of ln(1/fasting insulin), the slope and its 95% CI for each glycemic category did not equal zero and were negative. For example, among individuals with diabetes, the slope of regression was −0.8 (95% CI, −0.9 to −0.6). Secondary measures of β-cell function also were evaluated for hyperbolic relationships between components. The hyperbolic relationship of IGI and 1/HOMA-IR was poorer than IGI and 1/fasting insulin; among those with diabetes, the slope of regression between IGI and 1/HOMA-IR was −0.6 (95% CI, −0.7 to −0.4). In contrast, the relationship improved slightly using the modified Matsuda Index instead of 1/fasting insulin (−0.9; 95% CI, −1.1 to −0.8). The hyperbolic relationships between $AUC_{ins/glu}$ and the insulin sensitivity measures were similar to or better than those between IGI and the various insulin sensitivity measures. The weakest relationship with $AUC_{ins/glu}$ was found with 1/HOMA-IR.

No interactions were found between DI$_o$ and sex, age, BMI, or waist circumference. Polytomous logistic regression was used to determine the odds of each hyperglycemic status category compared with NGT for incremental changes in DI$_o$, HOMA-IR, and other covariates. Regression results are shown in Table 2. DI$_o$ and HOMA-IR were each independently associated with glycemic status, as shown in model 1. The odds for each glycemic category compared with NGT were significantly lower for every SD increase in DI$_o$, both in prediabetes and in diabetes (each $P < 0.0001$). In particular, the odds ratio (OR) of diabetes compared with NGT was extremely small for each SD increase in DI$_o$. Almost no change in the magnitude of association between DI$_o$ and glycemic status was found after adjustment for age, for age, BMI, waist circumference, or for age, BMI, waist circumference, and family history (Table 2, models 2, 3, 4). In contrast to DI$_o$, the odds for any glycemic category compared with NGT were greater for every SD increase in HOMA-IR. Adjustment for age, BMI, waist circumference, and family history did not substantially change the magnitude of association between HOMA-IR and glycemic status.

Polytomous regression with secondary measures of β-cell function yielded more pronounced findings, with the relative contributions of β-cell function on glycemic status exceeding that of HOMA-IR. For the measure $AUC_{ins/glu}$ × modified Matsuda, which exhibited the best hyperbolic relationship between insulin secretion and insulin sensitivity, β-cell function was independently associated with glycemic status (iIFG: OR, 0.11; 95% CI, 0.07–0.16; iIGT: OR, 0.34; 95% CI, 0.25–0.46) and HOMA-IR was not associated with glycemic status (iIFG: OR, 0.94; 95% CI, 0.66–1.33; iIGT: OR, 1.16; 95% CI, 0.84–1.60).

CONCLUSIONS—This study underscores the importance of β-cell dysfunction relative to insulin resistance across glycemic status groups in Asian Indians, particularly iIFG and iIGT. Using an index of β-cell function relative to insulin sensitivity, DI$_o$, a highly significant difference in DI$_o$ was observed between NGT and iIFG or iIGT. A difference in insulin resistance, as measured by HOMA-IR, also was observed; however, the difference in mean HOMA-IR was greatest between IFG plus IGT and diabetes, whereas the greatest difference in mean DI$_o$ was between NGT and iIFG. Results

Table 2—*Standardized polytomous logistic regression estimates for the OR of each glycemic status group*

	Normal (reference) *n* =341	iIFG *n* = 200	iIGT *n* = 202	IFG plus IGT *n* = 270	Diabetes *n* = 251
Model 1					
DI_o	1	0.35 (0.22–0.54)‡	0.37 (0.24–0.57)‡	0.02 (0.01–0.04)‡	0.001 (0.001–0.001)‡§
HOMA-IR	1	1.56 (1.17–2.07)†	1.53 (1.15–2.03)†	1.97 (1.50–2.59)‡	1.91 (1.44–2.55)‡
Model 2					
DI_o	1	0.35 (0.22–0.54)‡	0.37 (0.24–0.57)‡	0.02 (0.01–0.04)‡	0.001 (0.001–0.001)‡§
HOMA-IR	1	1.69 (1.26–2.27)†	1.61 (1.20–2.15)†	2.18 (1.65–2.89)‡	2.14 (1.59–2.88)‡
Age	1	1.44 (1.20–1.74)†	1.21 (1.00–1.45)*	1.60 (1.32–1.93)‡	1.90 (1.52–2.38)‡
Model 3					
DI_o	1	0.35 (0.23–0.55)‡	0.37 (0.24–0.56)‡	0.02 (0.01–0.04)‡	0.001 (0.001–0.001)‡§
HOMA-IR	1	1.70 (1.23–2.33)†	1.53 (1.11–2.11)†	2.07 (1.52–2.81)‡	2.31 (1.66–3.22)‡
Age	1	1.46 (1.21–1.76)‡	1.20 (0.99–1.44)	1.59 (1.32–1.93)‡	1.85 (1.48–2.32)‡
BMI	1	1.11 (0.87–1.42)	0.98 (0.77–1.25)	1.06 (0.84–1.35)	0.71 (0.53–0.96)*
Waist	1	0.88 (0.70–1.11)	1.11 (0.88–1.41)	1.08 (0.85–1.37)	1.16 (0.87–1.55)
Model 4					
DI_o	1	0.36 (0.23–0.55)‡	0.37 (0.24–0.56)‡	0.02 (0.01–0.05)‡	0.001 (0.001–0.001)‡§
HOMA-IR	1	1.69 (1.23–2.33)†	1.53 (1.11–2.11)†	2.07 (1.52–2.81)‡	2.31 (1.66–3.22)‡
Age	1	1.47 (1.21–1.77)‡	1.20 (0.99–1.44)	1.62 (1.33–1.96)‡	1.84 (1.47–2.32)‡
BMI	1	1.11 (0.87–1.41)	0.98 (0.77–1.25)	1.06 (0.83–1.35)	0.71 (0.53–0.96)*
Waist	1	0.88 (0.70–1.12)	1.11 (0.88–1.41)	1.09 (0.86–1.39)	1.16 (0.86–1.55)
Family history	NI¶	NI¶	NI¶	NI¶	NI¶

Data presented as OR and 95% CI. *$P<0.05$. †$P<0.01$. ‡$P<0.001$. §OR and CI are <0.001. ¶Standardized ORs for family history are not interpretable.

from statistical modeling showed that the relative contributions of DI_o to iIFG and to iIGT were greater than those of HOMA-IR, even after adjustment for variables known to impact disease development, including age, BMI, waist circumference, and family history of diabetes. These findings suggest that despite conflicting studies (17–20) in Asian Indians, a decrease in β-cell function may be a primary etiological factor in the development of type 2 diabetes in this ethnic group.

DI_o was selected as the primary measure of β-cell function for several reasons. First, the measure agrees with the biological constructs known for β-cell function, because secretion of insulin is measured relative to the prevailing levels of insulin sensitivity in the body (21). Second, mathematical confirmation in studies with more rigorous designs has demonstrated a hyperbolic relationship of the two components (i.e., insulin secretion and insulin sensitivity) (23,32). Third, autocollinearity between the components of DI_o is unlikely to drive the hyperbolic relationship, as described elsewhere (31). Fourth, longitudinal studies have indicated that DI_o is a good measure of disease processes related to β-cell function, because it predicts the development of future diabetes (23). In addition to DI_o, alternative measures of β-cell function were analyzed. Like another study, our results suggest that ($AUC_{ins/glu}$ × modified Matsuda Index) and ($AUC_{ins/glu}$ × 1/fasting insulin) should be examined further as potentially strong measures of DI_o (32). Across measures of β-cell function, similar findings indicated that the relative contribution of β-cell function toward glycemic status categories was greater than that of insulin resistance.

Studies that have examined β-cell function in various ethnic groups (i.e., β-cell function defined as insulin secretion with adjustment for insulin sensitivity within individuals) (12,21) have shown alternative patterns across glycemic phenotypes compared with those found in the current study. In a study of 1,399 normal-weight Japanese adults, those with iIFG were found to have somewhat preserved β-cell function using the ratio of change in AUC for plasma insulin to plasma glucose ($\Delta AUC_{PI}/\Delta AUC_{PG}$) from 0 to 120 min of the OGTT after adjustment of the Matsuda Index. This measure of the disposition index was reduced in iIFG (mean ± SEM, 7.1 ± 0.5; $P < 0.05$; with iIFG defined as fasting plasma glucose 6.1–7.0 mmol/L) compared with the NGT group (9.7 ± 0.2). A more extreme and statistically significant difference was detected in the iIGT (mean ± SEM, 2.7 ± 0.2) and the combined IFG plus IGT (2.1 ± 0.2) groups compared with both the NGT and iIFG groups ($P < 0.05$) (33). In another study of 1,272 Chinese adults, a decline in early phase DI_o ($\Delta AUC_{PI}/\Delta AUC_{PG}$ at 30 min, adjusted with the Matsuda Index) was found in both iIFG (fasting glucose 5.6–7.0 mmol/L) and iIGT—both significantly lower than NGT—but DI_o in iIGT also was significantly lower than DI_o in IFG (both $P < 0.05$) (34). The current study showed that early-phase DI_o was significantly reduced in iIFG as in iIGT. These findings are supported by the longitudinal Inter99 study involving Danish adults. Early-phase DI_o was measured at both baseline and 5-year follow-up using fasting insulin, 30-min insulin, and 30-min plasma glucose adjusted for insulin sensitivity index (10). The authors reported that DI_o was lower in those with incident iIGT and IFG plus IGT than in those with incident iIFG (fasting plasma glucose 6.1–6.9 mmol/L) after 5 years of follow-up. However, among all individuals with NGT at baseline (n = 3,145), those who would later develop iIFG (NGT to iIFG) had lower mean DI_o at baseline compared with those who would eventually develop iIGT (NGT to iIGT). These results suggest that individuals who develop iIFG already have significantly lower DI_o in normoglycemia, and the reduction in DI_o during normoglycemia may be as severe or more severe in those who eventually develop iIFG compared with iIGT. In

populations in which the progression toward diabetes is particularly rapid, the level of DI_o in normoglycemia may be an important factor related to disease risk. Future multiethnic studies are needed to determine if and how β-cell decline varies by ethnicity and to what degree differences lie between iIFG and iIGT.

This study has several important strengths. It contains a large, well-characterized, community-based sample stemming from the screening of almost 20,000 people and, therefore, was not limited to hospital- or clinic-based samples. All cases of diabetes were newly diagnosed. A hyperbolic relationship was found between insulin sensitivity and insulin secretion using linear regression to estimate $\ln(\Delta I_{0–30} / \Delta G_{0–30})$ as a function of ln(1/fasting insulin), indicating appropriate use of the disposition index as a measure of β-cell function. We used standardized regression to enable comparison of variables that were measured in different units and, consequently, to directly compare the relative contributions of β-cell function and HOMA-IR to the development of prediabetes and diabetes.

The limitations of this study include its cross-sectional design, limiting further inquiry regarding temporality, and the degree of representation of the sample, because results may not be generalizable to other populations (e.g., other racial/ethnic groups). In addition, all subjects had a random blood glucose level of ≥6.1 mmol/L before receiving the OGTT and, therefore, the NGT group may not be representative of normoglycemia. However, if the NGT group had normal random blood glucose levels, even greater differences between NGT and iIFG or iIGT groups would be expected. Therefore, our results provide conservative estimates of the lower β-cell function and higher insulin resistance in iIFG and iIGT relative to NGT groups. We excluded seven individuals for having negative or zero values of the insulinogenic index, values considered biologically implausible; however, this number comprises a very small percentage of the total sample (0.5%), smaller than reported in another study (2.7%) (23). Only one OGTT test was performed for each participant, and thus the classification of some individuals may have changed if the OGTT had been performed a second time. Another limitation pertains to the use of an OGTT-derived measure of β-cell function, rather than estimates based on the glucose clamp technique or the frequently sampled intravenous glucose tolerance test as used by Bergman et al. (21), who showed that insulin secretion had a hyperbolic relationship (i.e., y = constant/x) with the existing state of insulin sensitivity. The findings here, using the measure of DI_o for β-cell function, are consistent with several other studies that used euglycemic clamps and intravenous glucose tolerance tests. These studies have shown that poor insulin secretion begins sometime during normoglycemia (35,36). Also, they have highlighted that potential differences in β-cell dysfunction may exist between IFG and IGT phenotypes (37–39), particularly that impairment of β-cell function may occur in iIFG at least as much as in iIGT.

Although the disposition index was originally based on intravenous sampling techniques, an OGTT-derived measure has been shown to be valid (23) and may include additional benefits in the study of β-cell function. The hyperbolic relationship between insulin sensitivity and insulin secretion has been demonstrated using OGTT data, indicating that DI_o is a valid measure of β-cell function and is highly predictive of 10-year incidence of diabetes (23). Several metabolic factors, such as glucose disposition, differ between oral and intravenous glucose loads as related to different responses in the liver and in the periphery and, thus, OGTTs may probe important physiological processes in glucose metabolism that cannot be studied through intravenous testing. Finally, OGTTs are easy to perform in populations, making them more convenient for epidemiological studies in which recruitment of sufficiently large study samples can correct for within-subject variability (23,31,40). The minimum sample size needed to detect a 20% change when using the insulinogenic index is 181 (40), a number far exceeded by the sample size of the current study. Thus, DI_o is a valid, informative, and practical approach to the study of β-cell function.

Using a robust measure of β-cell function, the current study provides evidence that those in any category of dysglycemia, including iIFG and iIGT, have lower β-cell function compared with those in the NGT category. This study also showed that insulin resistance was greater across all categories of dysglycemia compared with NGT. However, the relative contribution of insulin resistance was not as great as that of β-cell function in any given glycemic status group. As such, the primary prevention and control of diabetes will require strategies to preserve β-cell function and reduce β-cell decline.

In conclusion, our data demonstrate markedly reduced β-cell function among Asian Indians with mild dysglycemia. These abnormalities cannot be attributed to differences in age, adiposity, insulin sensitivity, or family history. Prospective studies are needed to further investigate the relative roles of β-cell dysfunction and insulin resistance in the early natural history of diabetes.

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L.R.S. analyzed data, wrote the manuscript, drafted tables and figures, and reviewed and revised the manuscript. M.B.W. and H.R. researched data and reviewed and revised the manuscript. M.K.A. and J.B.E.-T. reviewed and revised the manuscript. L.S.P. contributed to analysis, discussion, and reviewed and revised the manuscript. V.M. contributed to analysis, discussion, and reviewed and revised the manuscript. K.M.V.N. contributed to concept, design, and analysis, and reviewed and revised the manuscript. L.R.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Chapter 6: Beta-cell function and insulin resistance in prediabetes and normoglycemia

Abstract

Objective - We previously showed that reduction in beta-cell function and increases in insulin resistance are quite apparent in mild dysglycemia among Asian Indians from Chennai, India. Here, we examine the pattern of changes in beta-cell function and in insulin sensitivity across a continuum of glycemia among Asian Indians who have not developed type 2 diabetes.

Research Design and Methods - 1,285 individuals without known diabetes were screened in the **D**iabetes **C**ommunity **L**ifestyle **I**mprovement **P**rogram in Chennai, India. Individuals had a 75g OGTT with glucose and insulin measured at 0, 30, and 120 min. Measures included insulin resistance (HOMA-IR), insulin sensitivity (1/fasting insulin), and beta-cell function ($DI_o = [\Delta I_{0\text{-}30} / \Delta G_{0\text{-}30}] \times [1/\text{fasting insulin}]$). Piecewise linear spline modeling, a regression technique that fits a sequence of regression lines, was used. Knots were created at every 0.25 mmol/L of blood glucose (i.e., with separate knots for fasting glucose [mmol/L] and 2-hour glucose [mmol/L]) and every 0.2% of HbA1c. The association of glycemia (independent variable) and DI_o (dependent variable) was evaluated as follows: spline models with combinations of 1, 2, and 3 knots were compared to linear models without splines. We assessed model fit using the Akaike Information Criterion (Akaike IC), and we tested the presence of significant differences between piecewise linear spline models and linear models without splines using the log

likelihood ratio (LR). Through these techniques, we identified significant change points (i.e., glycemic values containing changes in linear rate) across glycemia.

Results - We empirically identified fasting glucose 5.0 mmol/L (90 mg/dL), 5.25 mmol/L (95.03 mg/dL), and 6.25 mmol/L (113.13 mg/dL) as the three change points in the association between fasting glucose and square root DI_o (LR $p = 0.0406$). For 2-hour glucose, two change points were identified 5.25, 5.75 mmol/L (95, 104 mg/dL) representing change in the rate of estimated DIo at very low 2-hour blood glucose concentration levels. While a third point at 7.5 mmol/L (135.75 mg/dL) did not meet the $p<0.05$ requirement for the LR test, it appeared to have importance in the spline analysis. No specific change points for HbA1c were identified for estimated DIo. Furthermore, no glycemic change points for any of the glycemic measures were identified for estimated HOMA-IR; rather, linear models without splines were found to have the best fit.

Conclusions - Data from this large, community-based study of Asian Indians suggest reduced beta-cell function appears at glycemic levels that are currently considered normoglycemia in addition to points across prediabetes. Further validation and longitudinal data are needed to corroborate these findings, which suggest that early preservation of beta-cell function may be important in seemingly healthy Asian Indians.

Introduction

Type 2 diabetes is a global problem, growing especially across low- and middle-income countries (1). A common clinical stage of disease development is prediabetes, a state of dysglycemia from which as many as 70% will eventually progress to diabetes (22). While it is known that two pathophysiological factors, insulin resistance and poor beta-cell function, lead to the development of dysglycemia, the extent of these features in preclinical stages of diabetes, such as prediabetes, is incompletely understood. We showed previously in both Asian Indian adults and youth that those with prediabetes already have substantial reductions in beta-cell function compared to normal glycemic individuals, above and beyond the decreases in insulin sensitivity (13; 85). Supported by epidemiologic studies (86-89) and genetic discoveries (90) in other populations, these findings suggest that the decline of beta-cell function plays an important role in glucose dysregulation at mild dysglycemia or even in normoglycemia, countering previously postulated 2-step mechanisms in which insulin resistance generally drives the conversion of normal glucose metabolism to prediabetes, and the resulting beta-cell dysfunction leads to diabetes in a substantial number of individuals (3; 91; 92).

Some studies over the past 20 years have examined the points along glycemia that are associated with diabetes, which, at times, prompted an evaluation of evolving definitions for prediabetes and diabetes (93; 94). These studies (e.g., in the Dutch population of the Hoorn Study and in young men in the Israeli Defense Forces) found that certain points of blood glucose (particularly those marking prediabetes or even normoglycemia) were more highly associated with diabetes later in life compared to lower values within normoglycemia. Few studies have examined the associations of

glycemia with the actual pathophysiological factors that lead to diabetes, namely poor beta-cell function and insulin resistance, to determine whether the rates of change are consistent across glycemic values are generally associated with good health or early phases of the disease (i.e., normoglycemia and prediabetes). Like the earlier studies that found associations between certain points of glycemia and increased rates of diabetes, new studies that characterize the rate of decline for beta-cell function or the rate of increase for insulin resistance could be useful in understanding the circumstances that propel or slow populations toward more severe conditions that lead to diabetes. Thus, characterizing the rate of decline in beta cell function or the rate of increase in insulin resistance along glycemia may improve the pathophysiological characterization of dysglycemia before diabetes.

While most studies on the etiology of diabetes have studied populations with prediabetes, some that have examined normoglycemic individuals showed steady decline in beta-cell function, detected within normal fasting plasma glucose levels above 4.0 mmol/L in Chinese study participants (38) and at 5.0 mmol/L in a small sample of both Caucasian and African-Americans (95; 96). Another smaller study from the Mayo Clinic did not detect any threshold along glycemia for reduced beta-cell function (97). In this study, we explore a spectrum of points along glycemia to determine whether changes in the rate of decline for beta-cell function exist. Likewise, we investigate potential changes in the rate of increasing insulin resistance along glycemia. We study these relationships in a cohort of Asian Indians studied previously (13). Asian Indians experiences high rates of diabetes (98) at younger ages and lower BMI values (9), and higher basal insulin levels (11) compared to European populations. The objective of this study was to

determine (a) whether pronounced changes in the reduction of beta-cell function or the increase in insulin resistance are apparent across glycemia and if so, (b) the precise values of blood glucose in Asian Indians where these pronounced changes in beta-cell function and insulin resistance may occur.

Research Methods

Study Participants

Men and women from Chennai, India were eligible for the Diabetes Community Lifestyle Improvement Program (D-CLIP), a primary prevention trial testing the effects of a step-wise model of diabetes prevention, including a culturally tailored, intensive lifestyle intervention, plus metformin when needed (14). A flow diagram of recruitment and participant exclusions are provided in Chapter 4, Figure 4-1. Participants were recruited using community-wide approaches at large-scale community events, housing/apartment complexes, local businesses, places of worship and educational institutions; through clinic records at the study site; and through direct referral by health care providers at the clinic. Community-based screening (n = 19,377) included a short survey, anthropometric measurements and a random capillary blood glucose test using a glucose meter (Lifescan, Johnson & Johnson, Milpitas, California, USA). Individuals who were pregnant, breastfeeding, with a history or evidence of heart disease, or with any other serious illness were excluded from the study. Screened volunteers who were 20 – 65 years; with a random capillary blood glucose of greater than or equal to 6.1 mmol/L (110 mg/dl); and without known type 2 diabetes were eligible for clinic-based screening (D-CLIP baseline testing), which included a 75g OGTT performed after an overnight fast.

All subjects at clinic-based screening provided informed consent between 2008 and 2011. Among the 1,285 individuals tested, fourteen participants were excluded for missing glucose or insulin measures of the OGTT at any time point (i.e., 0 or 30 or 120 minutes). An additional seven individuals were excluded for having negative or zero values of the insulinogenic index (IGI), a measure of the early insulin response in the OGTT (41), calculated as the ratio of change in insulin to the change in glucose from 0 to 30 minutes (i.e., $\Delta I_{0\text{-}30}/\Delta G_{0\text{-}30}$). The final number of participants included in the present analyses was 1,264. The study was approved by the Emory University Institutional Review Board and the Madras Diabetes Research Foundation Ethics Committee.

Study Procedures

The demographic, anthropometric and glucose tolerance data collected are described elsewhere (13; 14). Briefly, after an 8-hour overnight fast, subjects participated in a standard 75-g oral OGTT (WHO 1980) with plasma glucose and insulin sampled at 0, 30 and 120 minutes. Other collected data included demographics, body weight, height, waist circumference and family history of diabetes (defined as having one or more first degree relatives with type 2 diabetes). For body weight assessment, subjects were asked to wear light clothing and weight was recorded after shoes and heavy jewelry were removed. Height was measured with a stadiometer to the nearest cm with subjects standing upright without shoes. BMI was calculated as mass (kg) / height squared (m^2). Waist circumference was measured twice at the smallest horizontal girth between the costal margins and the iliac crests at minimal respiration using a non-elastic measuring tape and averaged. OGTT samples were collected in EDTA, separated and stored at -80^{o}C. Plasma glucose (hexokinase method) was measured on a Hitachi 912

Autoanalyzer (Hitachi, Mannheim, Germany) using kits supplied by Roche Diagnostics (Mannheim, Germany). Insulin concentrations were estimated using an electrochemiluminescence method (COBAS E 411, Roche Diagnostics, Mannheim, Germany). The intra- and inter- assay co-efficient of variation for the biochemical assays ranged between 3.1 to 7.6 per cent. Samples were processed in a laboratory accredited nationally by the National Accreditation Board for Testing and Calibration Laboratories and internationally by the College of American Pathologists.

Key Variables

Measures of glycemia were fasting glucose (mmol/L), 2-hr glucose (mmol/L), and HbA1c (%). Glycemia was limited to normoglycemia and non-diabetic hyperglycemia as defined by American Diabetes Association criteria (8), specifically -

Fasting plasma glucose. Normal fasting glucose (NFG, i.e., fasting plasma glucose <5.6 mmol/L [100 mg/dl]) and impaired fasting glucose (IFG, i.e., fasting plasma glucose 5.6–6.9 mmol/L [100-125 mg/dl]).

2-hour postload glucose. Normal glucose tolerance (NGT, i.e., 2-hour postload glucose < 7.8 mmol/L [140 mg/dl]) and impaired glucose tolerance (IGT, i.e., 2-hour postload glucose 7.8 –11.0 mmol/L [140-199 mg/dl]).

HbA1c. Normoglycemia was defined as HbA1c < 5.7%, and nondiabetic hyperglycemia was defined as HbA1c 5.7-6.5%.

Beta-cell function was measured using the oral disposition index, denoted as DI_o, calculated as IGI adjusted for insulin sensitivity: $DI_o = ([\Delta I_{0-30} / \Delta G_{0-30}] \times [1/\text{fasting}$

insulin]) (41). Insulin resistance was estimated using HOMA (HOMA-IR = [fasting insulin mU/L x fasting glucose, mmol/L]/22.5) (84).

Data Analysis

Analyses were performed using SAS 9.3 (SAS Institute, Cary, NC).The associations of glycemia (independent variable) and DI_o (dependent variable) or HOMA-IR (dependent variable) were evaluated using linear regression. Non-normally distributed variables were log-transformed as required to meet assumptions of regression. Piecewise linear splines, a regression technique that fits a sequence of regression lines (99; 100), was used to detect points along glycemia at which changes in linear rate of DI_o or of HOMA-IR occur. Splines are lines with join points (i.e., abscissa values) that indicate transition from one spline to the next, and these join points are often referred to as knots (101) or, here, as change points. We created separate spline terms for fasting glucose [mmol/L] and 2 hour glucose [mmol/L]). Spline terms were created with predetermined values at every 0.25 mmol/L along the spectrum of normoglycemia and prediabetes. Unique spline terms were also created at every 0.2% HbA1c. Next, for each variable of glycemia, spline models with every combination of 1, 2, and 3 spline terms were compared to linear models without spline terms. Model fit was assessed using the Akaike Information Criterion (Akaike IC). The model with the smallest Akaike IC indicated best fit (102). Log likelihood ratio (LR) tests determined whether piecewise spline models weere significantly different from simple linear models with continuous glycemia ($p<0.05$). Specific spline models that (a) had better fit than the simple linear model and (b) were significantly different from the simple linear model indicated where along glycemia the change points in the linear rate between glycemia and the dependent

variable (i.e., DI_o or HOMA-IR) occurred, if at all. We also visually inspected (i.e., graphically) the unadjusted, linear relationship of glycemia and estimated DI_o or estimated HOMA-IR through (a) categories of glycemia, with categories defined by every value of glycemia as a separate category (b) continuous glycemia, and (c) piecewise splines.

Results

Detailed demographic and anthropometric characteristics among the 1,264 individuals have been reported elsewhere (13). Briefly, among all participants, the mean age was 44.2 years (9.3), and 37% were female. According to specific World Health Organization cut-offs for Asians (12), 47% were overweight and 45% were obese. One-fifth had newly diagnosed diabetes (19.9%), more than half (53.2%) had prediabetes (15.8% with isolated IFG; 16.0% with isolated IGT; and 21.4% with IFG plus IGT). Mean fasting glucose was 5.8 mmol/L (SD 1.0), ranging from 3.8 to 13.9 mmol/L, whereas mean 2-hour glucose was 8.8 mmol/L (SD 3.1), ranging from 2.9 to 22.9 mmol/L. Mean HbA1C was 6.1% (SD 0.8), ranging from 4.5 to 15.3%. The geometric mean of DI_o was 1.30 $L/mmol_{glu}$ (geometric SD 2.35, range 0.017 to 86.30), and mean HOMA-IR was 3.4 [mU_{ins} x $mmol_{glu}/(L^2)$], (SD 2.1, range 0.5 to 27.6). Results from piecewise spline analyses are provided for DI_o and HOMA-IR below.

Change Points of Oral Disposition Index in Normoglycemia and Prediabetes

Fasting Glucose: Among all participants, 1,160 individuals had normoglycemia or prediabetes according to fasting glucose criteria only. One individual was excluded for biological implausible DI_o at the lowest value of fasting glucose, and 1,159 remained in

the analysis. Figures 6-1 and 6-2 graphically depict the linear relationship between fasting glucose and estimated DI_o (i.e., transformed using square root of DI_o). First, fasting glucose is shown as a continuous variable and next, as a categorized variable (i.e., at each fasting glucose value). Across the spectrum of increasing glycemia, DI_o decreased in a smooth fashion according to simple linear regression, or in a very jagged, continuous pattern when glycemia was treated categorically. Table 6-1 provides a summary of the models that fit the relationship best. The model with the lowest Akaike IC was the spline model with 3 change points at 5.0, 5.25, 6.25 mmol/L (90, 95, 113 mg/dL, Figure 6-3). Two other models with low Akaike ICs included a spline model with a change point at 6.5 mmol/L (117 mg/dL) and a spline model with 2 change points, 5.25 and 6.25 mmol/L (95, 113 mg/dL). The model with 3 change points was selected as the model with (a) best fit compared to simple linear model and that was (b) significantly different from the simple linear model using the LR test. As such, we determined that changes in the rate of decline of beta cell function may exist at 5.0, 5.25, 6.25 mmol/L across fasting glucose.

Two-hour glucose: Among 1029 individuals who had normoglycemia or prediabetes (i.e., based on 2-hr glucose values only), Figures 6-4 and 6-5 illustrate the linear relationships of continuous and categorized 2-hr glucose with DI_o. Table 6-2 provides a summary of the models that fit the relationship best, including the best spline models for 1, 2, and 3 change points. The model with the lowest Akaike IC that was also significantly different from the simple linear model was the spline model with change points at 5.25 and 5.75 mmol/L (95, 104 mg/dL, Figure 6-6). Another model with the next lowest Akaike IC contained 3 change points, 5.0, 5.25, 6.25 mmol/L (90, 95, 113 mg/dL). Across models

with 1 change point, the model with the lowest Akaike IC contained a change point at 7.5 mmol/L (135 mg/dL). The best fit model described above that also included change the point at 7.5 mmol/L was also statistically different than the simple linear model (Figure 6-7).

HbA1c: According to ADA criteria, 967 individuals had normoglycemia or prediabetes using HbA1c definitions. Figures 6-8 and 6-9 illustrate the simple linear relationship between HbA1c and estimated DI_o, with HbA1c defined as a continuous variable and as a categorized variable (i.e., at each HbA1c value), respectively. All models with any combination of splines fit more poorly than the simple, linear model of HbA1c and DI_o.

Change Points of HOMA-IR in Normoglycemia and Prediabetes

No change points for HOMA-IR were identified across fasting glucose, 2-hr glucose, or HbA1c. Figures 6-10 through 6-15 graphically depict the simple linear relationship between glycemia and estimated HOMA-IR and the linear relationship between glycemia after categorization each fasting value. The simple linear models for each measure of glycemia contained the best fit for estimated HOMA-IR.

Discussion

In this study, we explored a spectrum of points along glycemia to determine whether changes in the rate of decline for beta-cell function exist. Likewise, we investigated potential changes in the rate of increasing insulin resistance along glycemia. In this analysis, we empirically identified points along fasting glucose at which changes in linear rate of DI_o occur. These change points were found at fasting glucose 5.0 mmol/L (approximately 90 mg/dL), 5.25 mmol/L (95 mg/dL), and 6.25 mmol/L (113 mg/dL). Other measures of glycemia were also measured for potential change points. For

2-hour glucose, two change points were identified 5.25, 5.75 mmol/L (95, 104 mg/dL) representing change in the rate of estimated DI_o at very low 2-hr blood glucose concentration levels. While incorporating a third spline term at 7.5 mmol/L (135.75 mg/dL) did not meet the $p<0.05$ requirement for the LR test, it appeared to have importance in the spline analysis. No specific change points for HbA1c were identified for estimated DI_o. Furthermore, no change points for any of the glycemic measures were identified for estimated change in HOMA-IR; rather, linear models without splines were found to have the best fit.

These findings suggest that the decline in beta-cell function may accelerate at certain points along the pathogenesis of disease in this group of Asian Indians. Increases in fasting glucose were associated with steep declines in DI_o until 5.0 mmol/L (90 mg/dL). The decline in estimated DI_o decelerated between5.0 and 5.25 mmol/L (90 and 95 mg/dL) and then accelerated again after fasting glucose 5.25 (95 mg/dL). Finally, a steady, decelerated decline in DI_o was found starting at 6.25 mmol/L (113 mg/dL). Unlike fasting glucose, estimated DI_o appeared to have little (i.e., mild declines) until 2-hour glucose 5.25 mmol/L, where a steep decline was found until 5.75 mmol/L (104 mg/dL), followed by a less dramatic decline for larger values of DI_o. Therefore, the points of accelerated decline in DI_o were found not only in prediabetes, but also in normoglycemia. These findings highlight that poor beta cell function occurs extremely early (i.e., during normoglycemia) in the pathogenesis of disease.

A few other studies have examined whether change points in glycemia exist in the decline of beta-cell function. Our findings are supported by Godsland and colleagues who used intravenous glucose tolerance tests (IVGTTs) to measure first- and second-

phase insulin secretion in 466 non-diabetic, white men (i.e., fasting glucose was less than 7.0 mmol/L) using three approaches: (1) the circulating insulin response; (2) population parameter deconvolution analysis of plasma C-peptide concentrations; (3) a combined model including both insulin and C-peptide concentrations (95). They found that fasting plasma glucose change points for first-phase insulin secretion occurred at 4.97 (approximately 90 mg/dL), 5.16 (93 mg/dL), and 5.42 mmol/L (98 mg/dL) for each of the three approaches, respectively. In addition, the decline in beta-cell function along fasting plasma glucose occurred alongside changes in insulin sensitivity that were primarily dependent on age and BMI (95). They concluded that the onset of decline in first-phase secretion was in normoglyecmia, with the rate of decline for each approach as: (1) 3.8%, (2) 4.2%, and (3) 4.5% per 0.1 mmol/L increase in fasting plasma glucose (95). The present study agrees with these findings; we also identified change points for early insulin secretion at 5.0 mmol/L (90 mg/dL), and we did not find any specific change points for insulin resistance.

Other studies that have examined the rate of decline in beta-cell function along glycemia have shown alternative findings. One study that used a spline analysis (i.e., locally weighted robust scatterplot smoothing (LOWESS) splines) to fit scatter plot data of nondiabetic study participants (i.e., participants had fasting glucose < 126 mg/dl (<7 mm) or were free of prior diagnosis) did not find any change points across fasting glucose for decline in DI, measured by OGTT as net insulin sensitivity times total beta-cell responsively to glucose (97). This study was conducted in Caucasians. In a different study of nondiabetic (i.e., 2-hour glucose < 11.1 mmol/L) Mexican American and Japanese men and women, small increments in fasting plasma glucose within the normal

range were reported to be associated with a marked decline in DI_o (i.e., DI_o was calculated using OGTT C-peptide deconvolution for incremental area under the insulin curve divided by the incremental area under the glucose curve adjusted for the severity of insulin resistance). The investigators concluded that the rate of decrease in insulin secretion was 2.5% for every 1 mg/dL increase in fasting plasma glucose (103), a rate of decline similar to that found by Godsland and collegues (95). While they did not find change points along glycemia, they fit hyperbolic and exponential models of DI_o (dependent variable) with fasting plasma glucose (independent variable). Therefore, they used different modeling strategies from the ones used in the current analysis and still support our findings that the reduction in beta-cell function is pronounced in normoglycemia.

We found that 2-hour glucose at 5.25 and at 5.75 mmol/L (95, 104 mg/dL) contained changes in the rate of estimated DI_o. These results appear plausible; Defronzo (104) found in the Actos Now for Prevention of Diabetes study that when NGT participants with 2 –hour plasma glucose <5.55 mmol/L (<100 mg/dL) were defined as 100% normal, both insulin secretion and insulin sensitivity declined progressively across the spectrum of 2-hour glucose, however, the decline in insulin secretion was two- to threefold greater than the decline in insulin sensitivity. Nevertheless, the change points identified in the present study are rather low in the range of 2-hour glucose values, and thu,s more research is needed to verify the relevance of these change points in declining beta-cell function. A third point at 7.5 mmol/L (135.75 mg/dL) did not meet the $p<0.05$ requirement for the LR test, but it appeared to have importance in the spline analysis, and this point was in the high end of normoglycemia, just before the cut off for prediabetes.

Contrary to the study that reported no detectable change points in Caucasians (97), categorical analyses in 873 Korean adults have previously suggested that changes in the rate of decline for beta-cell function may lie somewhere between 133 and 145 mg/dL (42), and that beta-cell function is well-reduced by the time an individual is classified as IGT. Early phase insulin secretion decreased rapidly along the 12 increments of 2-jr postchallenge glucose (ranging from 2-hr glucose ≤ 112 mg/dL with n=76 to 2-hour glucose ≥354 mg/dL with n=71), and these changes were most prominent in the NGT stage. Compared to the normoglycemia group, the early phase insulin secretion levels of the subjects with prediabetes or diabetes were less than 50% when 2 hour glucose was over 145 mg/dL (42).

This study did not detect any change points along HbA1c for decline in DI_o or increase in HOMA-IR. While we found that beta-cell function and insulin resistance had a decreasing linear relationship with increasing HbA1c, data from OGTT data of 522 Mexican Americans found that DI_o (measured as change in AUC insulin secretory rate during the 120 minutes of OGTT divided by change in glucose and adjusted by the Matsuda Index) did not change significantly up to an HbA1c >5.7%, at which point a marked decrease in beta-cell function was detected (105). The authors did not specify how they detected a change at this specific point (e.g., splines, graphical visual inspection, etc.), and their analyses focused on categorical changes along HbA1c. Other findings from categorical analyses in Koreans have also pointed to HbA1c of 5.5-5.7% to be significantly different from referent values of <5.0% (42). A notable observation from the Mexican American study was that those with both normal glucose tolerance and HbA1c of less than 5.7% had beta-cell function comparable to that of subjects who had

both normal glucose tolerance and HbA1c = 5.7–6.4% (105). Subjects with IFG or IGT had a marked decrease in beta-cell function, independent of their HbA1c level (105). Such results provide evidence that OGTT derived states of hyperglycemia may be much more important tools for accurate identification of individuals with impaired glucose beta-cell function compared to HbA1c.

The limitations of this study include its cross-sectional design and its use of a convenience sample, albeit a community-wide sample. We only had a single blood drawing for each OGTT which might have introduced random measurement errors in determining fasting plasma glucose and other biochemical variables. This study was not designed to predict risk of poor beta-cell function or insulin sensitivity at any given point along glycemia. Rather, the purpose of the spline analysis was to characterize the overall decline of beta-cell function in normoglycemia and mild dysglycemia in this sample of Asian Indians, and so for this analysis, we focus on rate of change during glycemia before and after significant change points. The actual change points themselves may have some limitations regarding biological relevance because of the sharp bends (kinks) at the boundaries of splines (100). Nevertheless, spline cut points were selected based on model fit, not based on maximizing significance or size of estimates (e.g., selection of cut points based on size of risk for diabetes), an issue of concern in spline analysis (100). We detected considerable inter-individual variation in DI_o especially at the lower end of fasting plasma glucose concentrations. This variation is consistent with other papers estimating DI or insulin resistance based on glycemia (95; 97; 103). Given that we were most interested in examining the spectrum of glycemia between end points of the spectrum, our use of unrestricted splines was considered preferable (100).

This study has several important strengths. It contains a large, well-characterized, community-based sample stemming from the screening of almost 20,000 people. We have previously demonstrated a hyperbolic relationship between our measures of insulin secretion and insulin sensitivity (13), verifying the known biological relationship of these constructs. In the current analysis, we identify change points containing significant changes in the rate of decline (or rate of increase) across the pathophysiological mechanisms of diabetes. Changes in the rate are biologically plausible when considering the mechanics of insulin secretion; insulin is secreted in two phases and secretory pulses are necessary for the maintenance of hepatocyte insulin receptors (97; 106). By using spline analysis, a rigorous analytical technique that for the aims of this paper, the present analysis has advantages over traditional categorical analysis [(e.g., reduced power loss due to grouping and loss of within category variation of risk (unrealistic model of risk) (100); no discontinuity between category endpoints of categories (107)]. Thus, spline modeling may provide a better fit, taking into consideration the variation in the relationship between the independent and dependent variables, both within and between levels of the independent variable (101). We minimized modeling instabilities and bias by uniformly choosing a series of knots throughout glycemia, rather than relying on a few knots based on prediabetes definitions or other points along glycemia.

In summary, this study confirms that in this sample of Asian Indians, significant changes in the rate of reduced beta-cell function occur at glycemic points that are below currently-accepted cut off values for prediabetes. Our data derived from the OGTT showed beta-cell function decreased at 90 mg/dL, similar to findings from a previous IVGTT-based study where first-phase secretion began to decline in the range of 5.0 to 5.4

mmol/l and late-phase secretion at levels above 6.0 mmol/l (95). Thus, fasting plasma glucose may provide a discriminatory index of declining beta-cell function. Further supported by studies that have detected precise points along glycemia to predict heightened risk for diabetes outcomes (94; 108), such results suggest that beta-cell dysfunction is pronounced in normoglycemia and across a variety of ethnicities and nationalities, including Asian Indians, Japanese, Israelis, and others. Future research should explore whether normal fasting glucose concentrations can serve as a marker for the presence of beta-cell dysfunction, and if so, how this marker may vary across ethnic populations. Preliminary evidence supports this suggestion; Mexican Americans with fasting plasma glucose between 95 and 100 mg/dL already had lost 60% of their beta-cell function compared to subjects at 70 mg/dL (103). The Whitehall II Study also analyzed beta-cell function (i.e., HOMA-B) and insulin sensitivity (HOMA-S) over 10 years, and retrospective differences in beta-cell function and insulin sensitivity between diabetes and non-diabetes groups were apparent 6 years before diagnosis, even after accounting for age, sex, and ethnic origin (109). Longitudinal studies are needed to confirm the findings in this study and quantify the extent to which beta-cell function worsens during normoglycemia. These studies will be critical for understanding the implications of the reduced beta-cell function and increased insulin resistance that occurs in some populations across normoglycemia.

In conclusion, data from this large, community-based study of Asian Indians suggest reduced beta-cell function at glycemic levels that are currently considered normoglycemia. Significant changes in the rate of increasing insulin resistance along glycemia was not detected. These findings suggest that pronounced changes in beta-cell

decline can be detected at precise points across normal fasting glucose levels, results that warrant further consideration of the pathophysiological role of beta-cell function on elevations in glycemia. Future research should validate these findings with longitudinal and representative data across ethnic groups.

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Chapter 6 Tables and Figures

Figure 6-1. Estimated DI_o (95% CI) from fasting glucose in 1,159 individuals in the D-CLIP trial

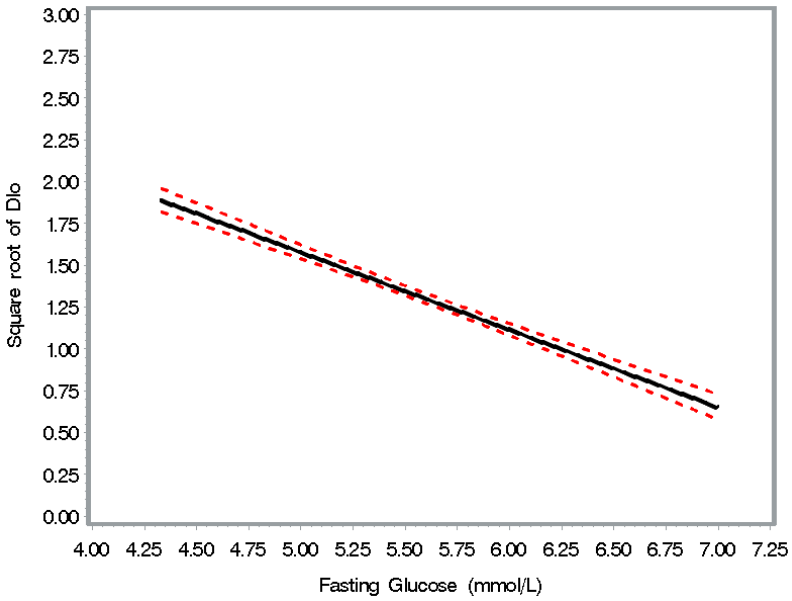

Figure 6-2. Estimated DI_o (95% CI) from categorical fasting glucose in 1,159 individuals in the D-CLIP trial

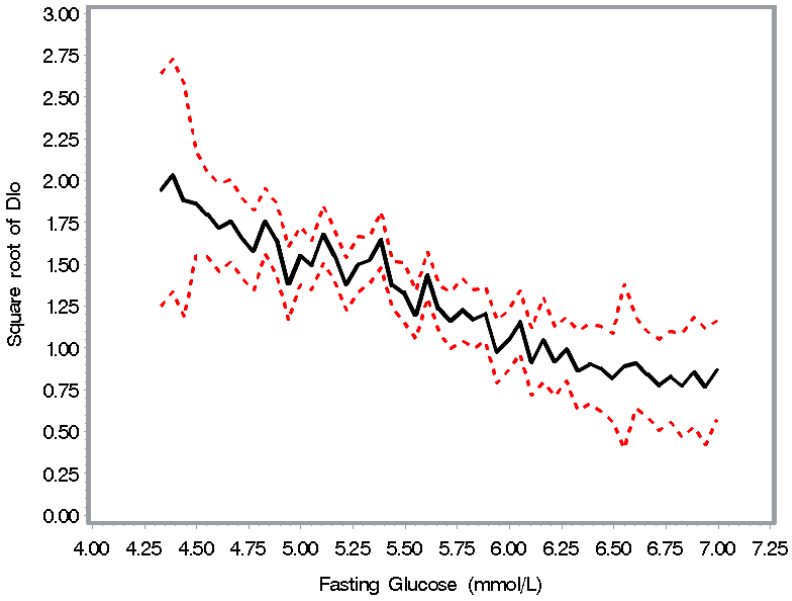

Table 6-1. Best fit models for fasting glucose and estimated DI_0 among D-CLIP participants with normal or elevated fasting glucose (n=1,159)

Characterization of Fasting Glucose	Model Details, Spline Change Points (mmol/l)	Akaike IC	LR test, p
Continuous	No splines	1738.6855	
Categorical	Every participant's fasting glucose value	1790.7149	
Splines			
1 Change Point	5.5 (99 mg/dL)	1740.6734	
	5.75 (104 mg/dL)	1739.9768	
	6.0 (108 mg/dL)	1738.4104	
	6.25 (113 mg/dL)	1736.9690	
	6.5 (117 mg/dL)	**1736.3338**	**LR=4.3518 df=1 P=0.0369**
	6.75 (122 mg/dL)	1737.1852	
2 Change Points	5.25, 6.0 (95, 108 mg/dL)	1737.1710	
	5.25, 6.25 (95, 113 mg/dL)	**1736.2809**	**LR=6.4046 df=2 p=0.0406**
	5.25, 6.5 (95, 117 mg/dL)	1736.4588	
	5.5, 6.0 (99, 108 mg/dL)	1736.7456	
	5.5, 6.25 (99, 113 mg/dL)	1736.3848	
	5.5, 6.5 (99, 117 mg/dL)	1736.8611	
3 Change Points	5.0, 5.25, 6.0 (90, 95, 108 mg/dL)	1736.5078	
	4.75, 5.25, 6.25 (86, 95, 113 mg/dL)	1736.6916	
	5.0, 5.25, 6.25 (90, 95, 113 mg/dL)	**1736.0891**	**LR=8.5966 df=3 p = 0.0351**
	4.75, 5.5, 6.25 (86, 99, 113 mg/dL)	1737.7989	
	4.75, 5.25, 6.5 (86, 95, 117 mg/dL)	1737.1063	
	5.0, 5.25, 6.5 (90, 95, 117)	1736.7196	

Figure 6-3. Best fit linear model of DIo (95% CI) from fasting glucose: change points at 5.0, 5.25, and 6.25 mmol/L

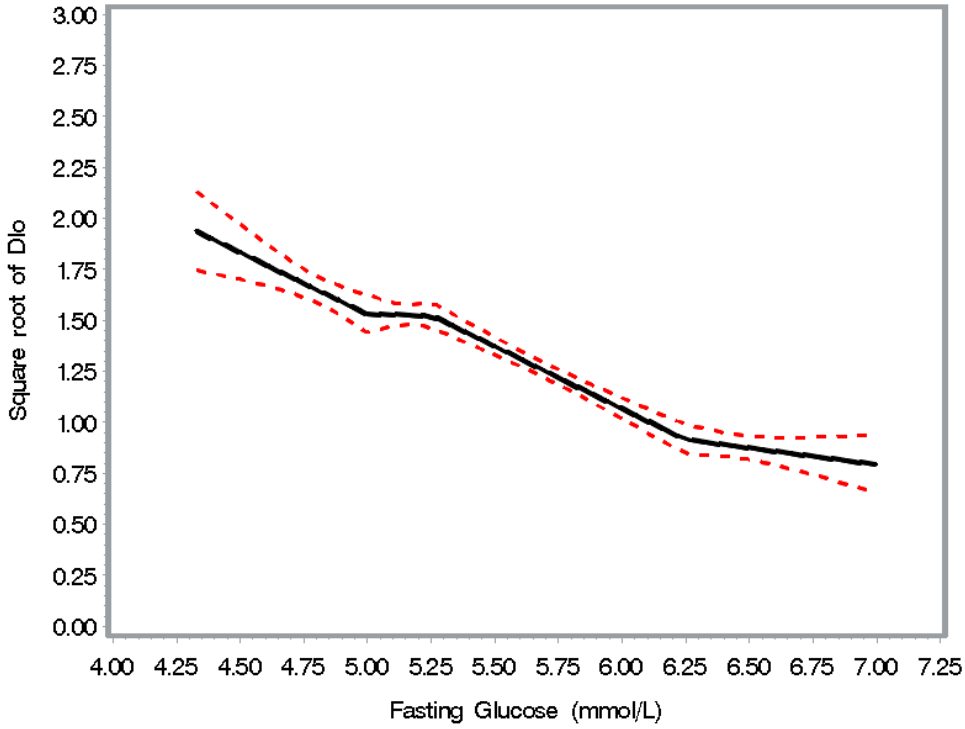

Figure 6-4. Estimated DI_o (95% CI) from two-hour glucose in 1,029 individuals in the D-CLIP trial

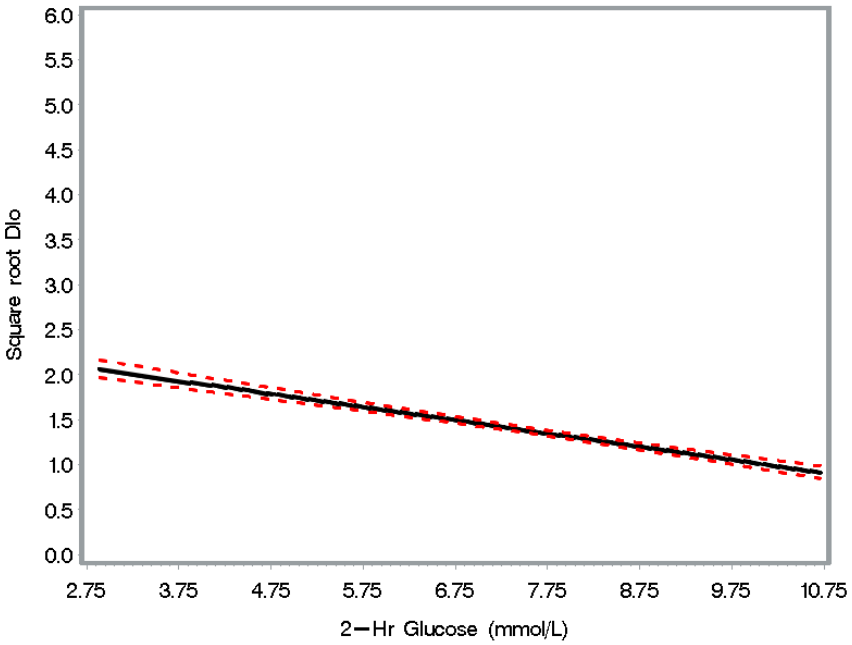

Figure 6-5. Estimated DI_o (95% CI) from categorical two-hour glucose in 1,029 individuals in the D-CLIP trial

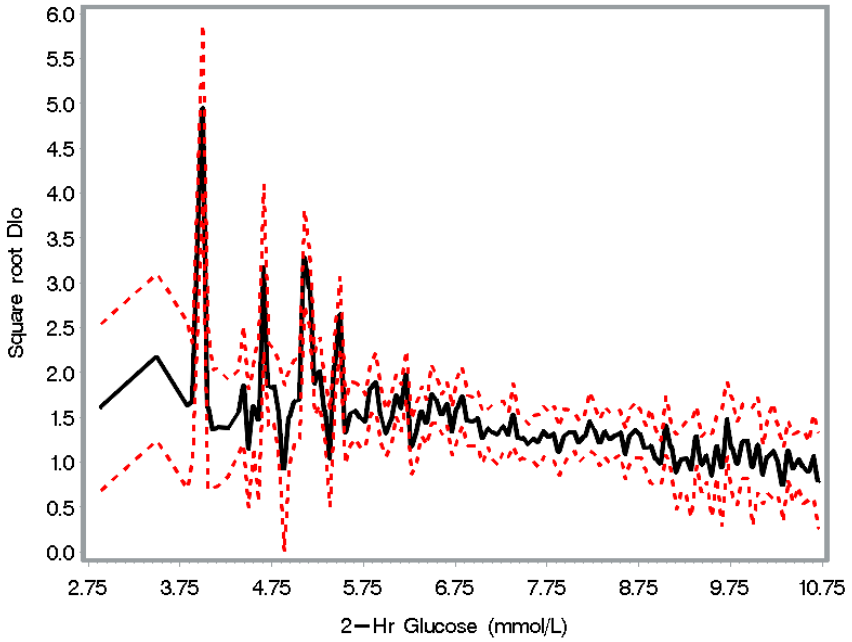

Table 6-2. Best fit models for two-hour glucose and estimated DI_0 among D-CLIP participants with normal or elevated two-hour glucose (n=1029)

Characterization of Two Hour Glucose	Model Details Spline Change Points (mmol/L)	Akaike IC	LR Test (p)
Continuous	---	1618.2969	
Categorical	Every participant's 2-hour glucose value	1644.5822	
Splines			
1 Change Point	7.25 (131 mg/dL)	1617.8760	
	7.5 (135 mg/dL)	**1617.5253**	**LR=2.7716, df=1, p=0.0959**
	7.75 (140 mg/dL)	1617.7788	
2 Change Points	4.75, 7.5 (86, 135 mg/dL)	1615.7188	
	5.0, 6.0 (90, 108 mg/dL)	1613.9607	
	5.0, 7.25 (90, 131 mg/dL)	1613.6262	
	5.0, 7.5 (90, 135 mg/dL)	1613.7580	
	5.25, 5.75 (95, 104 mg/dL)	**1610.0451**	**LR=12.252, df=2, p=0.0021**
	5.5, 5.75 (99, 104 mg/dL)	1611.9519	
3 Change Points	5.0, 5.75, 7.5 (90, 104, 135 mg/dL)	1614.1012	
	5.0, 7.25, 8.25 (90, 131, 149 mg/dL)	1614.6174	
	5.0, 7.5, 8.25 (90, 135, 149 mg/dL)	1613.4631	
	5.0, 7.75, 8.25 (90, 140, 149 mg/dL)	1613.3794	
	5.25, 5.5, 7.5 (95, 99, 135 mg/dL)	1611.0524	
	5.25, 5.75, 7.5 (95, 104, 135 mg/dL)	**1610.9259**	**LR=13.3712, df=3, p=0.0038**

Figure 6-6. Best fit model of estimated DI_0 (95% CI) with change points 5.5 and 5.75 mmol/L

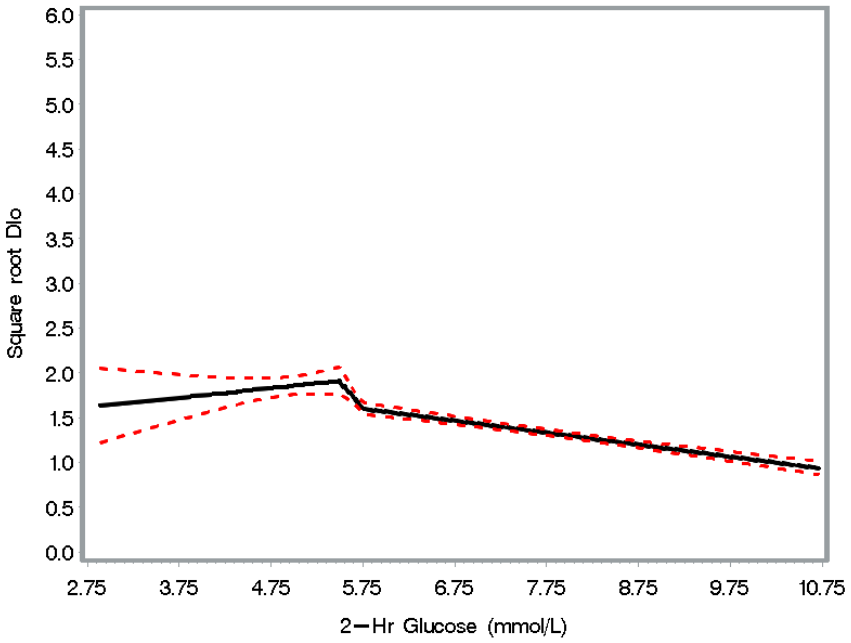

Figure 6-7. Another good model of estimated DI_0 (95% CI) with change points 5.5, 5.75, and 7.5 mmol/L

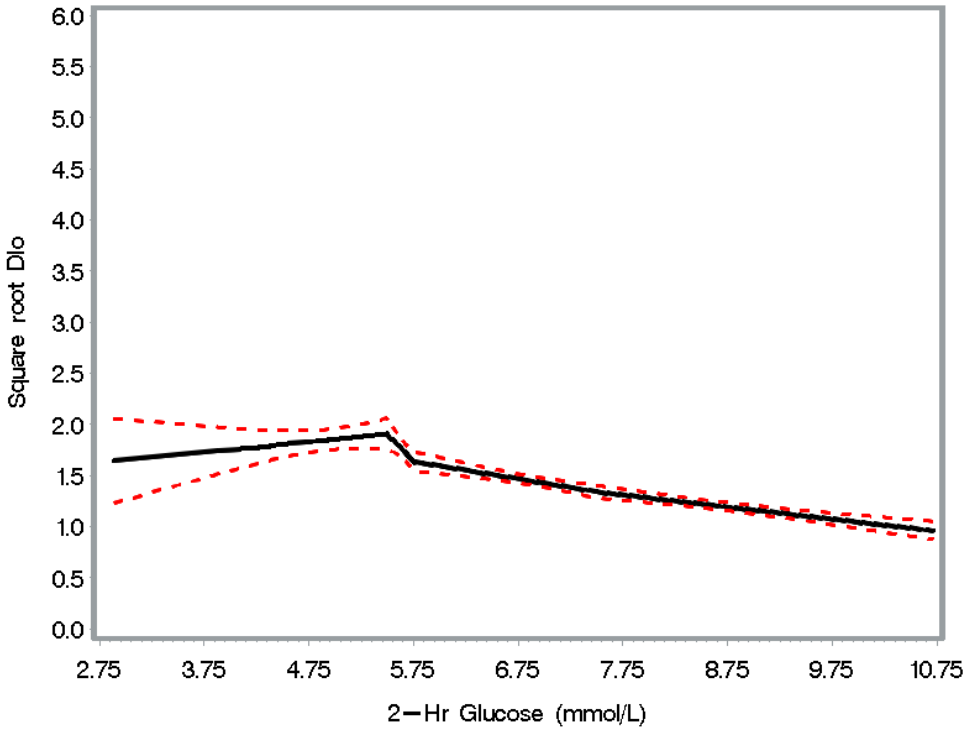

Figure 6-8. Estimated DI_o (95% CI) from HbA1c in 967 individuals in the D-CLIP trial – simple linear model

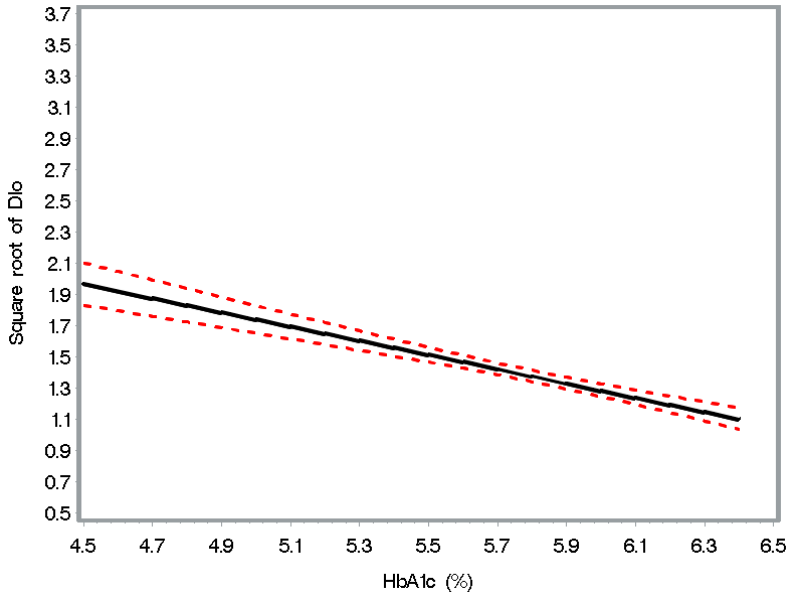

Figure 6-9. Estimated DI_o (95% CI) from categorized HbA1c in 967 individuals in the D-CLIP trial

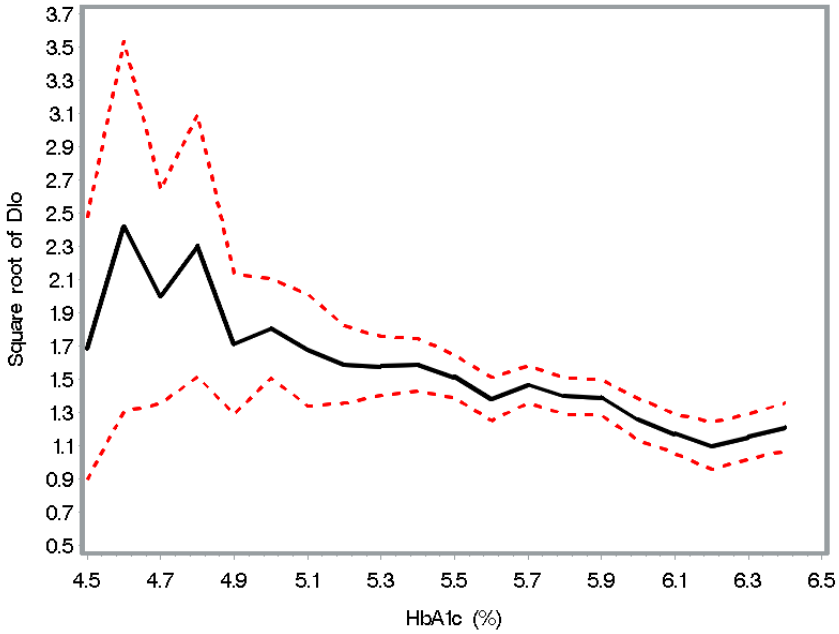

Figure 6-10. Estimated HOMA-IR (95% CI) from fasting glucose in 1,159 individuals in the D-CLIP trial

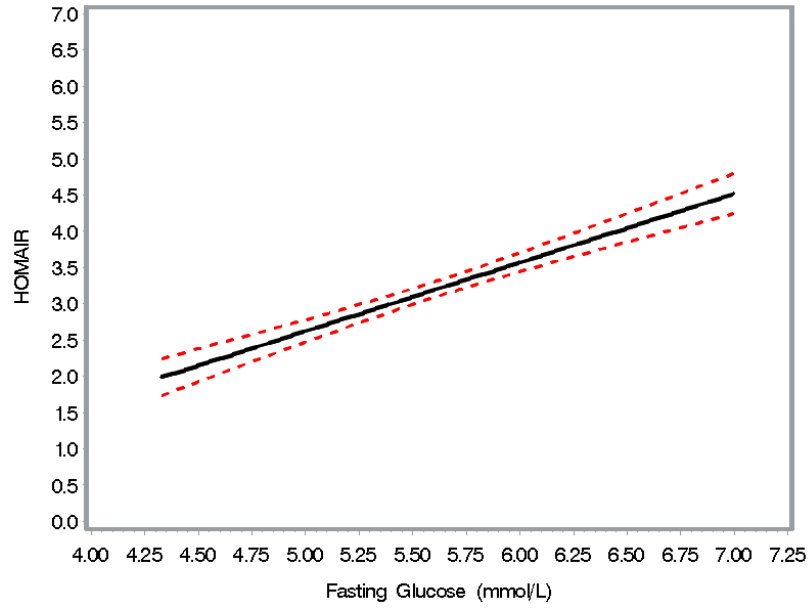

Figure 6-11. Estimated HOMA-IR (95% CI) from categorical fasting glucose in 1,159 individuals in the D-CLIP trial

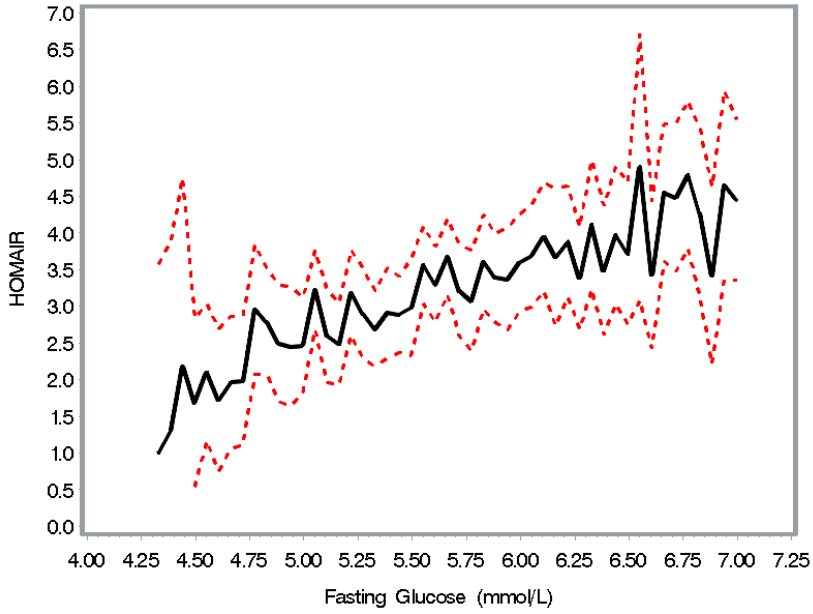

Figure 6-12. Estimated HOMA-IR (95% CI) from 2-hour glucose in 1,029 individuals in the D-CLIP trial

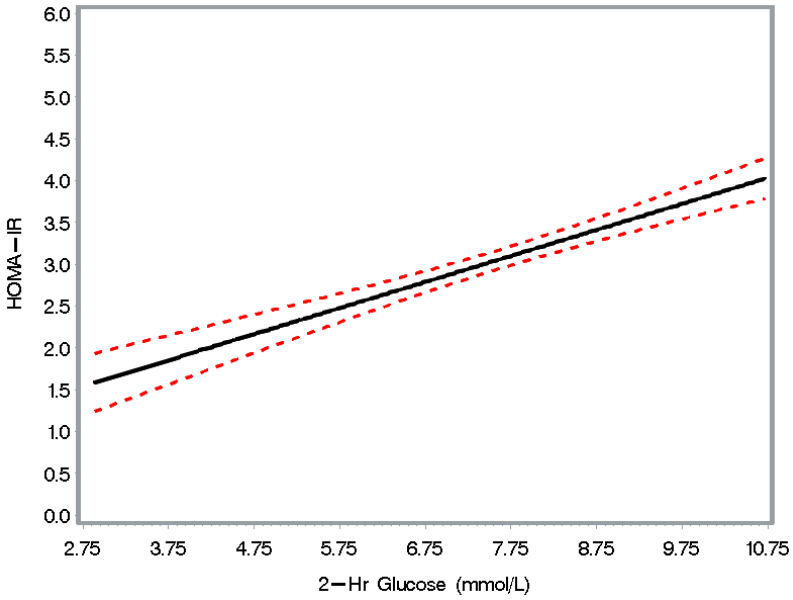

Figure 6-13. Estimated HOMA-IR (95% CI) from categorical 2-hour glucose in 1,029 individuals in the D-CLIP trial

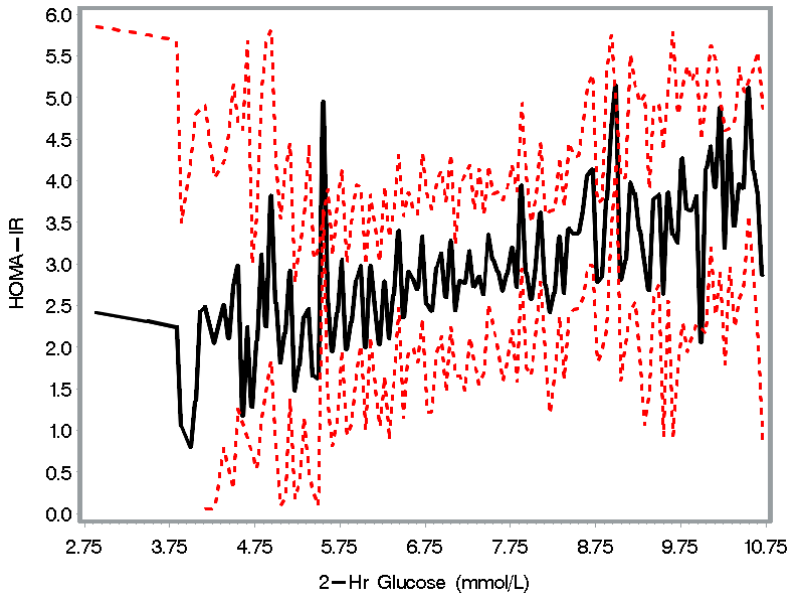

Figure 6-14. Estimated HOMA-IR (95% CI) from HbA1c in 967 individuals in the D-CLIP trial

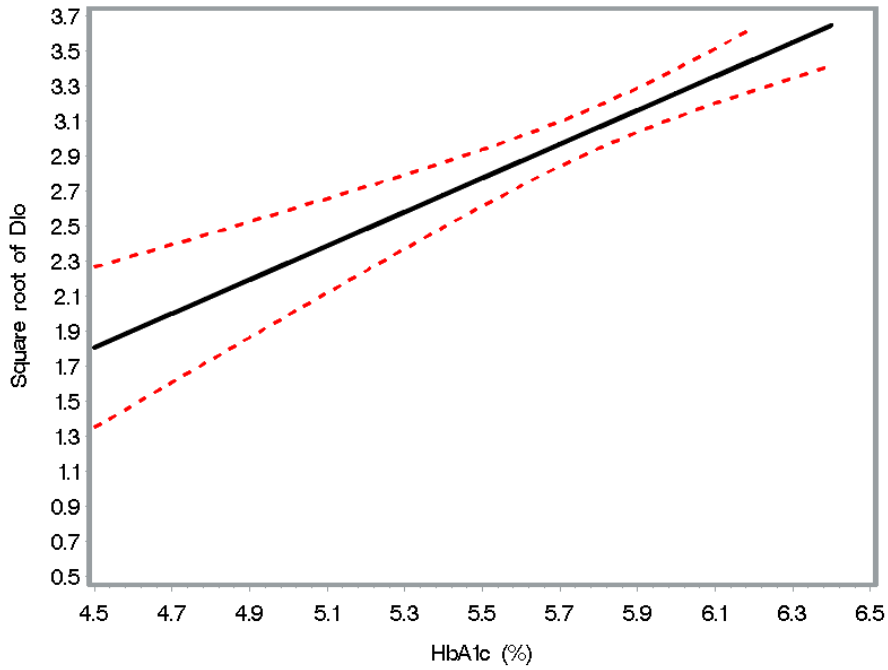

Figure 6-15. Estimated HOMA-IR (95% CI) from HbA1c in 967 individuals in the D-CLIP trial

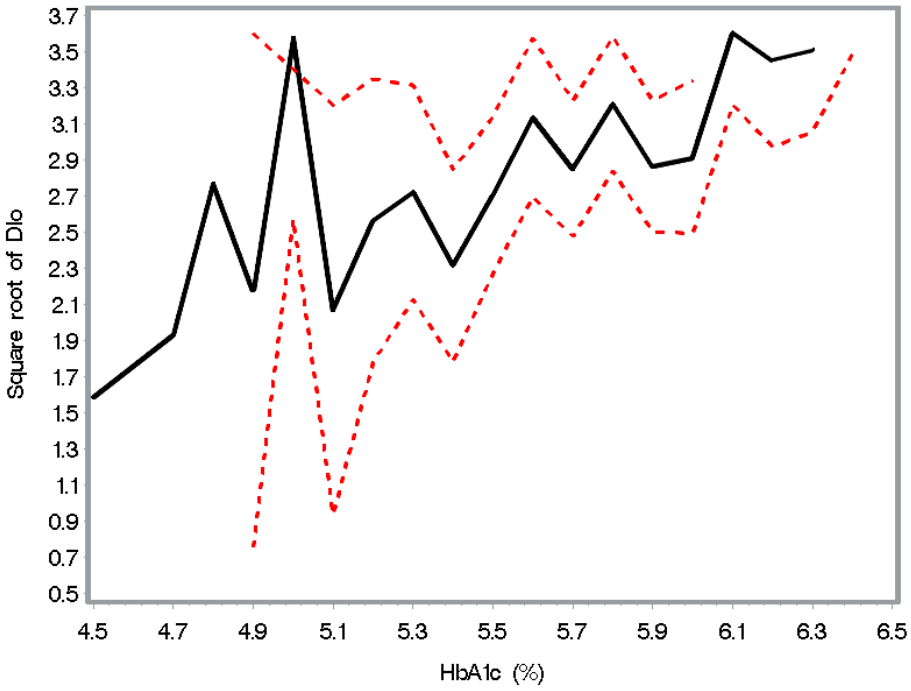

Table 6-3. Summary of results for piecewise linear spline regression

Glycemia	Best Fit Model for Estimated DI_o	Best Fit Model for Estimated HOMA-IR
Fasting Glucose	Linear spline model, change points: 5.0, 5.25, 6.25 mmol/L	Simple Linear Model
Two-hour glucose	Linear Spline Model, change points: 5.25, 5.75 mmol/L	Simple Linear Model
HbA1c	Simple Linear Model	Simple Linear Model

Chapter 7: Longitudinal Evidence for the Role of Reduced Beta-Cell Function on Glycemia in Asian Indians With Mild Dysglycemia

Abstract

Objective – We previously showed that the relative contribution of beta-cell function to impaired fasting glucose and to impaired glucose tolerance is greater than insulin resistance. Here, we examine the relative associations of baseline beta-cell function and baseline insulin sensitivity on glycemia at one year follow up among Asian Indians with prediabetes.

Research Design and Methods – 602 overweight individuals were enrolled in the **D**iabetes **C**ommunity **L**ifestyle **I**mprovement **P**rogram in Chennai, India. Most of these individuals had prediabetes (impaired fasting glucose [iIFG] and/or impaired glucose tolerance [iIGT]). The present study analyzes data from the first 474 individuals who returned for one-year follow up. At both baseline and follow up, individuals had a 75g OGTT with glucose and insulin measured at 0, 30, and 120 min. Other measures included insulin resistance (HOMA-IR), insulin sensitivity (1/fasting insulin), and beta-cell function ($DI_o = [\Delta I_{0-30} / \Delta G_{0-30}] \times [1/\text{fasting insulin}]$). The relative associations of baseline DI_o and baseline HOMA-IR on glucose levels at one year were determined through standardized linear regression, in which interaction testing and confounding assessment followed simple linear modeling.

Results – Mean age among 474 participants at one year follow up was 45.5 years (SD 8.94) and 63.1% were male. At baseline, 96.6% had prediabetes (144 [30.4%] iIFG; 135 [28.5%] iIGT; 179 [37.8%] combined IFG+IGT), 15 (3.1%) had diabetes, and 1 person (0.2%) had NGT. Adjusted for baseline fasting plasma glucose, baseline DI_o was significantly associated with fasting glucose at one year, even after accounting for treatment group, HOMA-IR, interactions, or potential confounders (DI_o p=0.0043, fully adjusted final model). Baseline HOMA-IR was associated with fasting glucose at one year, modified by family history (p=0.0261). For the outcome, 2-hour glucose at follow up, a significant interaction between baseline DI_o and waist circumference was apparent (p=0.057, final model), however, baseline HOMA-IR was not a significant predictor (p=0.510, fully adjusted final model). Finally, both baseline DI_o and baseline HOMA-IR were significantly associated with HbA1c at one year follow up (adjusted for baseline HbA1c) was highly significant at one year (HOMA-IR p=0.027; DI_o p=0.055 final model). Significant interactions in this final model existed between DI_o and waist circumference (p=0.028), HOMA-IR and waist circumference (p=0.098), and HOMA-IR and family history (p=0.013).

Discussion – These longitudinal findings support the importance of baseline beta-cell function and baseline HOMA-IR on 2-hour postchallenge glucose. Future studies will need to evaluate normoglycemic individuals at baseline to evaluate the relative contributions of beta-cell function and insulin resistance on long term fasting glucose levels or HbA1c. Future research should also explore the time course of beta-cell function decline, particularly how and when it begins to occur and how diabetes prevention strategies can prevent its decline.

Introduction

Type 2 diabetes is a problem affecting a wide variety of people – those from high and low income countries (6), those from rural and urban settings (110), and those from a variety of ethnicities (21; 111-114). While high levels of insulin resistance and inadequate beta-cell function have been reported to lead prediabetic individuals to diabetes (91; 115), this area needs further research. We have recently shown that dramatic decreases in beta-cell function are already apparent in prediabetes among Asian Indians, and that beta-cell dysfunction may contribute more to prediabetes than the accompanying increases in insulin resistance (13; 85). These findings and those from other cross sectional studies (38; 103; 116; 117) and genetic discoveries (118) suggest that the decline of beta-cell function occurs even before any form of hyperglycemia sets in, countering generalized mechanisms which imply that insulin resistance drives the conversion of normal glucose metabolism to prediabetes, and that beta-cell dysfunction is an issue of concern primarily in the change from prediabetes to diabetes (3; 4; 91; 92).

Some studies have examined the pathophysiology of prediabetes and diabetes longitudinally by recruiting study participants in normoglycemia, impaired fasting glucose, or impaired glucose tolerance and following them over time. These studies in Caucasians (63; 89), Pima Indians (119), and Japanese Americans (41) suggest beta-cell dysfunction and insulin resistance are apparent during the early development of diabetes (i.e., during the transition from NGT to IGT) and worsen over time. Yet, no longitudinal studies have examined the effects of these factors in Asian Indians, a population with high basal insulin levels (11) experiencing high rates of type 2 diabetes (98) even at younger ages and lower BMI values (9) compared to other populations. Here, we build

upon our previous cross sectional analysis (13) to investigate the associations between pathophysiologic mechanisms of insulin resistance and beta-cell function with glycemia among prediabetic Asian Indians at one year of follow up.

Research Methods

Study Participants

The study sample consisted of men and women from Chennai, India who participated in screening for the Diabetes Community Lifestyle Improvement Program (D-CLIP). D-CLIP is a primary prevention trial testing the effects of a step-wise model of diabetes prevention, including a culturally tailored, intensive lifestyle intervention, plus metformin when needed (14). Community-wide approaches for screening included large-scale community events, housing/apartment complexes, local businesses, places of worship and educational institutions; through clinic records at the study site; and through direct referral by health care providers at the clinic. Community-based screening (n = 19,377) comprised of a short survey, anthropometric measurements and a random capillary blood glucose test using a glucose meter (Lifescan, Johnson & Johnson, Milpitas, California, USA). Screened volunteers who were 20 – 65 years old; with a random capillary blood glucose of greater than or equal to 6.1 mmol/L (110 mg/dL); and without known type 2 diabetes were eligible for clinic-based screening (D-CLIP baseline testing), which included a 75g OGTT performed after an overnight fast. However, individuals who were pregnant, breastfeeding, with a history or evidence of heart disease, or with any other serious illness were excluded from the study.

Of the individuals participating in community-based screening, 1,285 with random capillary glucose ≥ 6.1 mmol/L and who met other inclusion criteria (described above) were eligible for follow-up, clinic-based examination. Next, subjects who were also at high risk for developing diabetes (baseline fasting plasma glucose indicating IFG: 100–125 mg/dL and/or 2-hour post-load glucose indicating IGT: 140–199 mg/dL) and overweight (based on South Asian-appropriate cut-points (WHO ref) as BMI ≥23 kg/m2 and/or had a waist circumference ≥90 cm for men and ≥80 cm for women) were eligible for participation in the randomized control trial. A total of 599 individuals were randomized to the intervention arm or to the standard of care control arm.

The current work analyzes the first group of individuals who returned for a one-year follow up visit by December 2012 (n=491). Six of these individuals were excluded for having missing values for 0, 30, or 120 minute OGTT values for insulin or for glucose. Two individuals were excluded for having negative or zero values of one –year data for the insulinogenic index (IGI), a measure of the early insulin response in the OGTT (41), calculated as the ratio of change in insulin to the change in glucose from 0 to 30 minutes (i.e., $\Delta I_{0\text{-}30}/\Delta G_{0\text{-}30}$). Nine other individuals were excluded for having missing OGTT data (i.e., glucose or insulin at 0, 30, 120 minutes) or having negative or zero values of IGI at baseline, and thus, a final sample size of 474 individuals was available for the current analysis. The study was approved by the Emory University Institutional Review Board and the Madras Diabetes Research Foundation Ethics Committee.

Study Procedures

The demographic, anthropometric and glucose tolerance data collected are described elsewhere (14). Briefly, after an 8 hour overnight fast, subjects participated in a standard 75-g oral OGTT (83) with plasma glucose and insulin sampled at 0, 30 and 120 minutes. Other collected data included demographics, body weight, height, waist circumference and family history of diabetes (defined as having one or more first degree relatives with type 2 diabetes). For body weight assessment, subjects were asked to wear light clothing and weight was recorded after shoes and heavy jewelry were removed. Height was measured with a stadiometer to the nearest cm with subjects standing upright without shoes. BMI was calculated as mass (kg) / height squared (m^2). Waist circumference was measured twice at the smallest horizontal girth between the costal margins and the iliac crests at minimal respiration using a non-elastic measuring tape and averaged. OGTT samples were collected in EDTA, separated and stored at -80^{o}C. Plasma glucose (hexokinase method) was measured on a Hitachi 912 Autoanalyzer (Hitachi, Mannheim, Germany) using kits supplied by Roche Diagnostics (Mannheim, Germany). Insulin concentrations were estimated using an electrochemiluminescence method (COBAS E 411, Roche Diagnostics, Mannheim, Germany). The intra- and inter-assay co-efficient of variation for the biochemical assays ranged between 3.1 to 7.6 per cent. Samples were processed in a laboratory accredited nationally by the National Accreditation Board for Testing and Calibration Laboratories and internationally by the College of American Pathologists.

Key Variables

Measures of glycemia were fasting glucose (mmol/L), 2- hr glucose (mmol/L), and HbA1c (%). These measures were collected at baseline and again at one-year follow up. Beta-cell function was measured using the oral disposition index, denoted as DI_o, calculated as IGI adjusted for insulin sensitivity: $DI_o = ([\Delta I_{0-30} / \Delta G_{0-30}] \times [1/\text{fasting insulin}])$ (41). Insulin resistance was estimated using HOMA (HOMA-IR = [fasting insulin mU/L x fasting glucose, mmol/L]/22.5) (84). Other covariates included age, sex, BMI, waist circumference, and family history of type 2 diabetes, as defined above.

Data Analysis

Analyses were performed using SAS 9.3 (SAS Institute, Cary, NC). Paired t-tests were used to compare continuous variables at baseline and one-year follow-up. The relative associations between baseline DI_o (independent variable) and baseline HOMA-IR (independent variable) with glycemia (outcome, defined as fasting glucose (mmol/L), 2-hr glucose (mmol/L), or HbA1c (%)) at one year were quantified using multivariate linear regression and were adjusted for baseline glycemia. Non-normally distributed variables were log-transformed as required to meet assumptions of regression, and variables were standardized to baseline values from the entire sample at baseline.

Interaction effects were tested between all baseline covariates (treatment group, age, BMI, waist, family history, sex) and baseline DI_o. Interaction effects were also tested between all baseline covariates and baseline HOMA-IR. All interaction terms were modeled, and backward elimination was used to remove insignificant ($p < 0.1$) interaction terms, one at a time. Following interaction testing, confounding was assessed by identifying models which contained parameter estimates of DI_o within 10% of the

gold standard model (i.e., the model with all significant interaction terms and all potential confounders) and which had the smallest SE around the parameter estimate.

Results

At baseline, mean age among 474 participants was 44.5 years (SD 8.9), 63.1% were male. Mean BMI was 27.8 (SD 3.6), mean waist circumference was in the overweight range (women 89.3 cm [SD 8.6]; men 97.7cm [SD 7.7]). In total, 96.0% of the study sample were overweight by Asian cut offs for BMI or by waist circumference at baseline. In addition, 96.6% had prediabetes at baseline (144 [30.4%] iIFG; 135 [28.5%] iIGT; 179 [37.8%] combined IFG+IGT); 15 (3.1%) had diabetes, and 1 person (0.2%) had NGT. Mean fasting glucose was 5.7 mmol/L (SD 0.5 mmol/L, range 4.3 to 7.0 mmol/L) or 102.7 mg/dL. Mean 2-hour glucose was 8.3 mmol/L (SD 1.5 mmol/L, range 2.9 to 11.4 mmol/L) or 149.5 mg/dL. Mean HbA1c was 6.0% (SD 0.5, range 4.5 to 8.9%).

As of May 2013, data for 474 participants with one-year of follow up were available (additional analyses with full study sample of n=599 will be completed in winter of 2014). Mean age among these participants at one year follow up was 45.5 years (SD 8.94) and 63.1% were male. At one year, 153 (32.3%) had normal glucose tolerance, 268 (56.5%) had prediabetes (96 isolated IFG, 74 isolated IGT, 98 IFG and IGT combined), and 53 (11.2%) had diabetes. Among all participants, 239 were randomized to the intervention arm, and 235 were randomized to the control arm.

Table 7-1 provides mean changes during one year follow up with both treatment groups combined. BMI decreased slightly by -0.47 kg/m2 ($p<0.0001$), but no statistically

significant change was found in waist circumference (+1.47 cm, p=0.5712). All glucose measures during the OGTT decreased. Net change was -0.1 mmol/L for 0 minutes; -0.23 mmol/L for 30 minutes; and -0.24 mmol/L for 120 minutes (p = 0.0009, 0.0015, 0.0174, respectively). Among the OGTT insulin measures, 2-hour insulin decreased by -65.83 pmol/L (p=0.0119), whereas basal and 30-minute insulin levels did not significantly change (-1.69 pmol/L, p = 0.3879; +0.47 pmol/L, p=0.6358, respectively). IGI values decreased by -15.77 $pmol_{ins}/mmol_{glu}$ (p=0.0088), insulin sensitivity values increased (+0.0008 L/pmol, p=0.0209 for 1/fasting insulin and +0.85 $((L^2)/mmol_{glu} \times pmol_{ins})$, p<0.0001 for Matsuda index). The overall DI_o increased (+1.12, p=0.0001) and HOMA-IR did not significantly change (-0.07, p=0.4252).

Multiple linear regression was used to determine relative associations of standardized DI_o and standardized HOMA-IR with the dependent variable, fasting glucose at one-year follow up. Table 7-2 provides simple, exploratory models, and Table 3 provides final selected models after interaction testing and confounding assessment. DI_o was significantly associated with fasting glucose at one year, even after accounting for treatment group, HOMA-IR, and potential confounders (p=0.007, Table 7-2). Interaction testing of all covariates (treatment group, age, BMI, waist, family history, sex) with both DI_o and with HOMA-IR, identified a statistically significant interaction between HOMA-IR and family history (Table 7-3, p=0.0261). After a subsequent confounding assessment, age and BMI were dropped from the model, and the final model indicated that both DI_o and HOMA-IR were important predictors of the 1-year fasting glucose. Age had no effect on the model's R^2 when kept or removed from the model. Furthermore, BMI improved the model's R^2 by only 0.0021.

Tables 7-4 and 7-5 provide exploratory and final selected models, respectively, for the dependent variable, 2-hour post challenge glucose at one year follow up. DI_o was a significant predictor of 2-hour glucose at one year follow up when modeled by itself, with HOMA-IR, and with other covariates ($p<0.0001$, Table 7-4). HOMA-IR was not statistically significant in these models, nor in final models (Table 7-5). An interaction was found between DI_o and waist circumference, and after confounding assessment, the final model did not include age or family history, which contributed little to the model's overall R^2 (full model, 0.239; model without age, 0.239; model without age or family history, 0.236). Tables 7-6 and 7-7 provide both simple, exploratory models and final, standardized models after interaction testing and confounding assessment for the dependent variable, HbA1c at one year follow up. DI_o was a significant predictor across all models (Table 7-6), and an interaction was found between DI_o and waist circumference ($p=0.027$).

Discussion

This longitudinal study in Asian Indians examined the relationship of baseline DI_o and baseline HOMA-IR with three different glycemic outcomes: fasting glucose, 2-hour glucose, and HbA1c. Findings suggested that that disturbances in beta-cell function is highly associated with future post-challenge glucose levels. Baseline DI_o was significantly associated with fasting glucose, 2-hour postchallenge glucose, and HbA1c at one year follow up, even after accounting for treatment group, HOMA-IR, interactions, or potential confounders. Baseline HOMA-IR was significantly associated with fasting glucose and HbA1c at follow up, but it was not a significant predictor of 2-hour glucose at follow up. As such, these findings not only highlight differences in beta-cell function

and insulin resistance across impaired fasting glucose and impaired glucose tolerance, but also suggest that beta-cell function could play an even more comprehensive or central role in the degradation of glucose metabolism compared to insulin resistance.

Several other longitudinal studies support our findings of the relative associations of poor beta-cell function and insulin resistance on future glycemic outcomes. In studies of Caucasians (63; 87; 89) and Japanese Americans (41), individuals who eventually developed hyperglycemia had lower levels of beta-cell function and insulin sensitivity at baseline. Among 3,145 normoglycemic Danish individuals who were followed for 5 years in the Inter99 study, OGTT-derived measures of insulin sensitivity and beta-cell function [insulin sensitivity index (ISI), HOMA-Insulin Sensitivity (HOMA-IS), and DIo (i.e., change in insulin (0-30 minutes) /glucose (0-30 min) x ISI] were lower at baseline for those who progressed to hyperglycemia compared individuals who maintained NGT (89). These results have been further confirmed in intravenous studies. In Pima Indians, defects in beta-cell dysfunction and insulin resistance were apparent early during the development of diabetes (i.e., during the transition from NGT to IGT) and worsened over time toward diabetes (119). The disposition index (i.e., calculated from the clamp procedure, $AIR_g \times S_i$) decreased 31.5% during the transition from NGT to IGT ($P < 0.05$). Among Hispanics, non-Hispanic whites, and African Americans in the Insulin Resistance Atherosclerosis Study (IRAS), data over 5.2 years suggested that not only did insulin sensitivity decrease over time, but so did beta-cell function, measured by IVGTT (120). Our findings appear to corroborate these findings and provide longitudinal evidence of the important role of beta-cell function in the early stages of diabetes.

In the present study, while baseline beta-cell function was associated with fasting glucose, two hour glucose, and HbA1c at one year follow-up, the relative significance of beta-cell function to insulin resistance varied, with beta-cell function appearing to have the greatest relative association (i.e., compared to insulin resistance) with 2-hour glucose. At first, these results may appear surprising, as other studies have suggested that IFG and IGT are two distinct pathological mechanisms with IFG being a state of raised hepatic glucose output and a defect in early insulin secretion, whereas IGT characterized as a state of peripheral insulin resistance (121). However, the Inter99 study found that baseline insulin secretion (DI_o) was significantly impaired in normoglycemic individuals who subsequently progressed to isolated IFG, but during the development of isolated IFG, DI_o did not decrease further (89), and the authors suggest that progressive loss of beta-cell function occurred substantially in earlier stages of fasting glucose (i.e., during normoglycemia and before baseline). In other words, beta-cell function levels at baseline were already low. In contrast, among normoglycemic individuals in the same study who eventually developed isolated IGT, DI_o at baseline was not different from those who maintained NGT. Rather, small but significant declines in DI_o were observed upon development of isolated IGT, suggesting that a progressive, age-dependent loss of insulin secretion may be involved in the development of postchallenge hyperglycemia (89). Thus, in the present study, it is possible that the relative contributions beta-cell function on one year levels of fasting glucose and HbA1c would have been greater had the sample consisted of individuals with normoglycemia and not just prediabetes at baseline. Future analyses of this cohort that will include NGTs for longitudinal analysis may show that DI_o plays an important role in postload hyperglycemia, above and beyond insulin

resistance. Indeed, in a study of Japanese individuals not treated for diabetes, high normal HbA(1c) levels of 36-40 mmol/mol (5.4-5.8%) were associated with impaired insulin secretion without marked insulin resistance in Japanese individuals (122).

We found statistically significant effect modification between HOMA-IR and family history of diabetes on the outcome of fasting glucose at one-year and also on the outcome of HbA1c at one-year. These findings are supported by a population-based sample of Asian Indian Mauritians (123) along with a study of normoglycemic Chinese individuals in which family history was associated with HOMA-IR but not beta-cell function (124). Other studies have suggested that the offspring of those with diabetes have both impaired insulin sensitivity and first-phase insulin secretion (125; 126). We also found effect modification between baseline DI_o and baseline waist circumference on the outcome of 2-hour postchallenge glucose, along with similar findings for the outcome of HbA1c at one year follow up. DI has been previously associated with abdominal obesity (127) and ALT liver enzyme (128). Those with abdominal obesity may exhibit greater inflammation in adipose tissue (129), and inflammation may have independent associations with beta-cell function. Waist circumference and body fat distribution are highly associated with susceptibility to diabetes among Asians (9; 13), whereas other measures of obesity, such as BMI, are better predictors of disease in Europeans (32). Thus, waist circumference may represent both a form of obesity and disease risk that is more common in certain lines of inheritance (i.e., certain ethnic groups) while also representing risk affected by lifestyle and environmental factors (130).

This study contains several limitations. First, the convenience sample utilized in this study may not be generalizable to other populations. Study participants were

overweight and most had prediabetes, and therefore, we did not assess beta-cell function and insulin resistance in a sample with a complete spectrum of relevant, metabolic conditions, particularly in the normal range where decline in beta-cell function but not the increase in insulin resistance was previously found to be greatest (13). However, given these earlier findings, we believe that our results here regarding the relative importance of beta-cell function on one-year glucose levels may be a conservative one. These speculations will be formally assessed in early 2014, when analyses will be rerun with not only the complete sample of 599 individuals who were randomized in the D-CLIP trial, but also 213 normoglycemic individuals who participated in our cross sectional analysis at baseline (13) and for whom plans for follow up were recently added in other study protocols.

Another limitation is that measures of beta-cell function were derived from OGTTs. While measures were derived from OGTTs rather than estimates based on the glucose clamp technique or the frequently sampled intravenous glucose tolerance test used by Bergman and colleagues (35), the findings here, using the measure of DI_o for beta-cell function, are consistent with several other studies that used euglycemic clamps and intravenous glucose tolerance tests showing that poor insulin secretion begins sometime during normoglcyemia (39; 63; 119; 131; 132). Next, we only had a single OGTT for each participant at baseline and again at follow up which might have introduced random measurement errors in determining fasting plasma glucose and other biochemical variables. However, additional OGTTs were not feasible in this large-scale epidemiological study, and the large sample size in the present study sufficiently accounts for added variation around measures (41). Next, it is possible that individuals

who participate in the group lifestyle intervention may have changed their physical activity level, diet, and body composition more than those who were not in the high-intensity intervention, however, we adjusted for intervention status as well as changes in body composition, and thus, we believe that our results are reliable.

In addition to the aforementioned limitations, the present analysis was not cannot disentangle potential causes of reduced beta-cell function (i.e., inherent versus acquired); analyses were not designed to address these issues. Acquired beta-cell dysfunction may result from glucotoxicity, lipotoxicity, or beta-cell compensation prior to the onset of insulin resistance. Hyperglycemia and intolerance to non-esterified fatty acids have been associated with susceptibility to lipid-induced reduction in both insulin sensitivity and beta-cell function (133). However, alternative evidence suggests that insulin sensitivity and beta-cell function may be affected differentially. Insulin sensitivity, but not beta-cell function, was associated with ectopic fat depots in the pancreas (134). Our analyses included mild hyperglycemic individuals in whom acquired beta-cell dysfunction may have less impact than those further along in the pathogenesis of disease.

This study has several valuable strengths. It contains a large, community-based sample stemming from the screening of almost 20,000 people. We used a robust measure of beta-cell function that accurately represents the biological phenomenon of insulin secretion adjusted for prevailing levels of insulin sensitivity. This measure was tested and confirmed previously (13) for a hyperbolic relationship between insulin sensitivity and insulin secretion, indicating appropriate use of the disposition index as a measure of beta-cell function. We used standardized regressions to compare variables that were measured in different units, as such, to directly compare the relative contributions of

beta-cell function and HOMA-IR to the progression of glycemia. The design of this analysis is longitudinal, using one year of follow up to assess the association of baseline beta-cell function and insulin resistance on glycemic outcomes. All cases of diabetes were newly diagnosed, and only individuals with prediabetes at baseline were followed up (soon to include follow up of normoglycemic individuals). While changes in most metabolic measures were relatively small across the one-year follow up period, even small changes in plasma glucose and insulin levels may have consequences for glucose homeostasis (89), suggesting that these findings are biologically important.

Future longitudinal studies may want to examine additional factors for a comprehensive analysis of the pathophysiological factors contributing to diabetes and prediabetes. Additional factors to consider include the interplay of beta-cell function, insulin resistance, and other factors of metabolism, including incretins and adipocyte insulin resistance, or the impact of lifestyle interventions on beta-cell function and insulin resistance. Marini and colleagues utilized OGTT, IVGTT, and clamp techniques to show that the cross sectional associations of beta-cell function and insulin resistance were more important than impaired incretin effects (135). In a different cross sectional, multivariate analysis of insulin secretion, insulin sensitivity, hepatic insulin resistance, and adipocyte insulin resistance as independent variables and with incremental glucose AUC as the dependent variable, beta-cell function was the primary determinant of the glucose AUC, explaining 62% of the variance (104). While one longitudinal study in Asian Indian adults did not explicitly define beta-cell function using the more rigorous and biologically valid measure of the disposition index (35), the study did show that higher levels of the insulinogenic index combined with improved insulin sensitivity after a lifestyle

intervention was associated with the reversal of high-risk individuals from IGT to normoglycemia over 3 years (64), suggesting that this type of research may have important implications for disease prevention.

In conclusion, longitudinal findings from the current study support the importance of baseline beta-cell function in the role of changing fasting glucose, 2-hour postchallenge glucose, and HbA1c. The relative contribution of beta-cell function to 2-hour postchallenge glucose levels may be greater than that of insulin resistance. Future longitudinal studies should further explore beta-cell dysfunction in normoglycemia relative to other important biological factors related to type 2 diabetes and determine how diabetes prevention strategies can best preserve beta-cell function to prevent the evolution of diabetes early in the pathogenesis of disease.

Chapter 7 Tables and Figures

Table 7-1. One Year Change in Table Form, n=474

Characteristic	Baseline		Follow Up			Paired ttest	
	Mean	SD	Mean	SD	Change	t value	p
Age	44.45	8.89	45.53	8.94	1.07	21.85	<.0001
BMI (kg/m^2)	27.79	3.64	27.32	3.65	-0.47	-8.13	<.0001
waist circumference (cm)	94.60	9.01	96.07	56.15	1.47	0.57	0.5712
fasting glucose (mmol/l)	5.72	0.50	5.63	0.69	-0.1	-3.33	0.0009
30 min glucose (mmol/l)	9.77	1.39	9.54	1.62	-0.23	-3.19	0.0015
2 hour glucose (mmol/l)	8.31	1.52	8.06	2.39	-0.24	-2.39	0.0174
fasting insulin (pmol/l)	79.39	46.66	77.70	41.12	-1.69	-0.86	0.3879
30 min insulin (pmol/l)	533.96	335.98	539.30	307.37	5.34	0.47	0.6358
2 hour insulin (pmol/l)	888.80	582.25	822.97	614.48	-65.83	-2.52	0.0119
1/fasting insulin (l/pmol)	0.016	0.009	0.017	0.010	0.0008	2.32	0.0209
Insulinogenic Index, IGI ($pmol_{ins}/mmol_{glu}$)	135.52	143.84	119.75	87.06	-15.77	-2.63	0.0088
HOMA-IR ($mmol/L_{glu}$ x uIU/mL_{ins})	3.37	2.00	3.30	1.98	-0.07	-0.80	0.4252
Modified Matsuda ($(l^2)/mmol_{glu}$ x $pmol_{ins}$)	9.59	5.10	10.45	5.97	0.85	3.99	<.0001
Oral Disposition Index (l/mmol)[a]	1.36	1.90	1.52	2.08	1.12	3.90	0.0001

Table 7-2. Exploratory, standardized models of fasting glucose at 1 year (n= 474)

Model	Model Components	β	SE	p (t test)	R^2	p (F test)
Without DIo or HOMA-IR	Baseline fasting glucose	0.625	0.052	<.0001	0.232	<.0001
Models with DIo but not HOMA-IR	DIo	-0.477	0.078	<.0001	0.0737	<.0001
	DIo	-0.234	0.074	0.002	0.248	<.0001
	Baseline fasting glucose	0.570	0.055	<.0001		
	DIo	-0.226	0.074	0.002	0.258	<.0001
	Baseline fasting glucose	0.568	0.054	<.0001		
	Treatment	-0.135	0.055	0.014		
	DIo	-0.306	0.108	0.005	0.259	<.0001
	Baseline fasting glucose	0.563	0.055	<.0001		
	Treatment	-0.212	0.093	0.023		
	DIo x treatment	0.144	0.141	0.306		
Models with HOMA-IR but not DIo	HOMA-IR	0.079	0.034	0.020	0.011	0.0199
	HOMA-IR	0.017	0.030	0.572	0.233	<.0001
	Baseline Glucose	0.620	0.053	<.0001		
	HOMA-IR	0.014	0.030	0.646	0.243	<.0001
	Baseline Glucose	0.615	0.053	<.0001		
	Treatment	-0.142	0.055	0.011		
	HOMA-IR	0.022	0.037	0.556	0.243	<.0001
	Baseline fasting glucose	0.616	0.053	<.0001		
	Treatment	-0.106	0.112	0.344		
	HOMA-IR x treatment	-0.023	0.062	0.711		
DIo, HOMA-IR, baseline fasting glucose, and treatment	DIo	-0.229	0.076	0.003	0.258	<.0001
	HOMA-IR	-0.006	0.031	0.834		
	Baseline fasting glucose	0.569	0.055	<.0001		
	Treatment	-0.135	0.055	0.014		
DIo, HOMA-IR, baseline fasting glucose, and covariates	DIo	-0.205	0.075	0.007	0.283	<.0001
	HOMA-IR	-0.034	0.032	0.287		
	Baseline fasting glucose	0.569	0.055	<.0001		
	Treatment	-0.127	0.055	0.021		
	Age	0.004	0.029	0.897		
	BMI	-0.057	0.054	0.290		
	Waist	0.151	0.058	0.009		
	Sex	-0.257	0.098	0.009		
	Family History	0.106	0.057	0.063		

Table 7-3. Final standardized models of fasting glucose at 1 year follow up after interaction testing and confounding assessment (n= 474)

Model	Model Components	β	SE	p (t test)	R^2	p (F test)
Models with DIo, HOMA-IR, and significant interactions before confounding assessment	DIo	-0.2188	0.07535	0.0039	0.2906	<.0001
	HOMA-IR	-0.15458	0.06268	0.014		
	Baseline fasting glucose	0.58092	0.05466	<.0001		
	Treatment	-0.11762	0.05446	0.0313		
	Age	0.00146	0.02899	0.9598		
	BMI	-0.06174	0.05384	0.2521		
	Waist	0.16787	0.05801	0.004		
	Sex	-0.27696	0.09809	0.005		
	Family History	-0.13207	0.12068	0.2743		
	HOMAIR x Family History	0.15321	0.06866	0.0261		
Final Model (age and BMI removed)	DIo	-0.21618	0.07525	0.0043	0.2885	<.0001
	HOMA-IR	-0.15722	0.06257	0.0123		
	Baseline fasting glucose	0.58225	0.05405	<.0001		
	Treatment	-0.12268	0.05419	0.0241		
	Waist	0.1141	0.03385	0.0008		
	Sex	-0.19176	0.06423	0.003		
	Family History	-0.12994	0.12005	0.2797		
	HOMA-IR x Family History	0.15064	0.06853	0.0284		
Alternate model (only age removed)	DIo	-0.21871	0.07525	0.0038	0.2906	<.0001
	HOMA-IR	-0.15467	0.06259	0.0138		
	Baseline fasting glucose	0.58132	0.05404	<.0001		
	Treatment	-0.11751	0.05436	0.0311		
	BMI	-0.06205	0.05344	0.2462		
	Waist	0.1682	0.05758	0.0037		
	Sex	-0.27731	0.09774	0.0047		
	FamHx	-0.13264	0.12003	0.2697		
	HOMA-IR x Family History	0.15333	0.06854	0.0258		

Table 7-4. Exploratory standardized models of two-hour glucose at 1 year (n= 474)

Model	Model Components	β	SE	p (t test)	R^2	p (F test)
Without DIo or HOMA-IR	Baseline 2-hour glucose	1.995	0.201	<.0001	0.174	<.0001
Models with DIo but not HOMA-IR	DIo	-1.843	0.267	<.0001	0.092	<.0001
	DIo	-1.251	0.258	<.0001	0.213	<.0001
	Baseline 2-hour glucose	1.730	0.203	<.0001		
	DIo	-1.221	0.257	<.0001	0.223	<.0001
	Baseline 2-hour glucose	1.714	0.202	<.0001		
	Treatment	-0.482	0.194	0.013		
	DIo	-1.531	0.372	<.0001	0.225	<.0001
	Baseline 2-hour glucose	1.720	0.202	<.0001		
	Treatment	-0.788	0.329	0.017		
	DIo x treatment	0.572	0.498	0.251		
Models with HOMA-IR but not DIo	HOMA-IR	0.252	0.117	0.032	0.010	0.032
	HOMA-IR	0.102	0.108	0.343	0.175	<.0001
	Baseline 2-hour Glucose	1.968	0.203	<.0001		
	HOMA-IR	0.091	0.107	0.399	0.187	<.0001
	Baseline 2-hour glucose	1.948	0.202	<.0001		
	Treatment	-0.517	0.199	0.010		
	HOMA-IR	0.085	0.134	0.526	0.2433	<.0001
	Baseline 2-hour glucose	1.947	0.202	<.0001		
	Treatment	-0.543	0.400	0.176		
	HOMA-IR x treatment	0.016	0.222	0.942		
DIo, HOMA-IR, baseline 2-hour glucose, and treatment	DIo	-1.236	0.265	<.0001	0.223	<.0001
	HOMA-IR	-0.027	0.108	0.806		
	Baseline 2-hour glucose	1.718	0.203	<.0001		
	Treatment	-0.484	0.195	0.013		
DIo, HOMA-IR, baseline 2-hour glucose, and covariates	DIo	-1.197	0.266	<.0001	0.233	<.0001
	HOMA-IR	-0.061	0.114	0.593		
	Baseline 2-hour glucose	1.685	0.204	<.0001		
	Treatment	-0.455	0.195	0.020		
	Age	0.019	0.103	0.857		
	BMI	-0.271	0.193	0.162		
	Waist	0.426	0.207	0.040		
	Sex	-0.576	0.351	0.102		
	Family History	0.233	0.203	0.254		

Table 7-5. Final standardized models of 2-hour glucose at 1 year follow up after interaction testing and confounding assessment (n= 474)

Model	Model Components	β	SE	p (t test)	R^2	p (F test)
Models with DIo, HOMA-IR, and significant interactions before confounding assessment	DIo	3.473	2.423	0.152	0.239	<.0001
	HOMA-IR	-0.077	0.114	0.501		
	Baseline 2-hour glucose	1.700	0.203	<.0001		
	Treatment	-0.434	0.195	0.027		
	Age	0.016	0.103	0.879		
	BMI	-0.289	0.193	0.135		
	Waist	0.718	0.255	0.005		
	Sex	-0.605	0.350	0.085		
	Family History	0.243	0.203	0.231		
	DIo x Waist	-0.482	0.248	0.053		
Final Model with DIo, HOMA-IR, covariates, and significant interactions (age and family history removed)	DIo	3.366	2.419	0.165	0.236	<.0001
	HOMA-IR	-0.075	0.114	0.510		
	Baseline 2-hour glucose	1.709	0.203	<.0001		
	Treatment	-0.438	0.195	0.025		
	BMI	-0.287	0.192	0.135		
	Waist	0.712	0.254	0.005		
	Sex	-0.615	0.349	0.079		
	DIo x Waist	-0.474	0.248	0.057		
Models with DIo, HOMA-IR, covariates, and significant interactions (age removed only)	DIo	3.478	2.420	0.151	0.239	<.0001
	HOMA-IR	-0.077	0.114	0.501		
	Baseline 2-hour glucose	1.702	0.203	<.0001		
	Treatment	-0.433	0.195	0.027		
	BMI	-0.292	0.192	0.128		
	Waist	0.721	0.254	0.005		
	Sex	-0.609	0.349	0.082		
	Family History	0.239	0.201	0.234		
	DIo x Waist	-0.482	0.248	0.053		

Table 7-6. Exploratory standardized models of outcome HbA1c at 1 year (n= 474)

Model	Model Components	β	SE	p (t test)	R^2	p (F test)
Without DIo or HOMA-IR	Baseline HbA1c	0.513	0.031	<.0001	0.368	<.0001
Models with DIo but not HOMA-IR	DIo	-0.374	0.059	<.0001	0.077	<.0001
	DIo	-0.167	0.051	0.001	0.382	<.0001
	Baseline HbA1c	0.484	0.032	<.0001		
	DIo	-0.161	0.051	0.002	0.388	<.0001
	Baseline HbA1c	0.486	0.032	<.0001		
	Treatment	-0.078	0.038	0.040		
	DIo	-0.178	0.075	0.017	0.388	<.0001
	Baseline HbA1c	0.485	0.032	<.0001		
	Treatment	-0.095	0.065	0.144		
	DIo x treatment	0.031	0.098	0.755		
Models with HOMA-IR but not DIo	HOMA-IR	0.083	0.026	0.001	0.022	0.0012
	HOMA-IR	0.039	0.021	0.062	0.373	<.0001
	Baseline HbA1c	0.505	0.031	<.0001		
	HOMA-IR	0.037	0.021	0.078	0.379	<.0001
	Baseline HbA1c	0.506	0.031	<.0001		
	Treatment	-0.082	0.038	0.032		
	HOMA-IR	0.028	0.026	0.277	0.379	<.0001
	Baseline HbA1c	0.506	0.031	<.0001		
	Treatment	-0.120	0.077	0.122		
	HOMA-IR x treatment	0.024	0.043	0.578		
DIo, HOMA-IR, baseline HbA1c, and treatment	DIo	-0.148	0.052	0.005	0.389	<.0001
	HOMA-IR	0.023	0.021	0.287		
	Baseline HbA1c	0.484	0.032	<.0001		
	Treatment	-0.077	0.038	0.044		
DIo, HOMA-IR, baseline HbA1c, and covariates	DIo	-0.142	0.052	0.007	0.397	<.0001
	HOMA-IR	0.017	0.022	0.437		
	Baseline HbA1c	0.470	0.033	<.0001		
	Treatment	-0.075	0.038	0.050		
	Age	0.033	0.021	0.112		
	BMI	-0.016	0.038	0.666		
	Waist	0.037	0.041	0.368		
	Sex	-0.044	0.069	0.525		
	Family History	0.063	0.040	0.112		

Table 7-7. Final standardized models of HbA1c at 1 year follow up after interaction testing and confounding assessment (n= 474)

Model	Model Components	β	SE	p (t test)	R^2	p (F test)
Models with DIo, HOMA-IR, and significant interactions before confounding assessment	DIo	0.971	0.499	0.052	0.411	<.0001
	HOMA-IR	0.356	0.162	0.029		
	Baseline HbA1c	0.456	0.033	<.0001		
	Treatment	-0.074	0.038	0.052		
	Age	0.033	0.021	0.113		
	BMI	-0.012	0.038	0.759		
	Waist	0.139	0.062	0.026		
	Sex	-0.037	0.069	0.593		
	Family History	0.245	0.085	0.004		
	DIo x Waist	-0.114	0.051	0.027		
	HOMA-IR x Waist	-0.025	0.015	0.099		
	HOMA-IR x Family History	-0.118	0.048	0.015		
Final Model with DIo, HOMA-IR, covariates, and significant interactions (BMI and sex removed)	DIo	0.958	0.497	0.055	0.410	<.0001
	HOMA-IR	0.357	0.161	0.027		
	Baseline HbA1c	0.459	0.032	<.0001		
	Treatment	-0.076	0.038	0.047		
	Age	0.033	0.020	0.108		
	Waist	0.122	0.051	0.018		
	Family History	0.250	0.084	0.018		
	DIo x Waist	-0.112	0.051	0.029		
	HOMA-IR x Waist	-0.025	0.015	0.098		
	HOMA-IR x Family History	-0.120	0.048	0.013		
Models with DIo, HOMA-IR, covariates, and significant interactions (Sex removed)	DIo	0.959	0.498	0.055	0.410	<.0001
	HOMA-IR	0.358	0.162	0.027		
	Baseline HbA1c	0.458	0.033	<.0001		
	Treatment	-0.076	0.038	0.046		
	BMI	0.033	0.020	0.107		
	Waist	0.004	0.025	0.888		
	Sex	0.121	0.052	0.021		
	Family History	0.250	0.084	0.003		
	DIo x Waist	-0.112	0.051	0.029		
	HOMA-IR x Waist	-0.025	0.015	0.098		
	HOMA-IR x Family History	-0.120	0.048	0.013		

Chapter 8: Discussion

Summary of Findings

Complemented by findings that Asian Indians in the United States are at high risk of type 2 diabetes (136), the body of work presented here provides a detailed analysis of the pathophysiological mechanisms of diabetes in Asian Indians from Chennai, India. Using three different analytical techniques of cross sectional and longitudinal data, the major findings of this dissertation are as follows: (1) decreases in beta-cell function were markedly apparent between NGT and prediabetes (**Chapters 5, 7**); changes in the rate of decline in beta-cell function were detected at 5.0, 5.25, 6.25 mmol/L (90, 95, 113 mg/dL) for fasting glucose and 5.25, 5.75, and 7.5 mmol/L (95, 104, and 135 mg/dL) for two-hour postchallenge glucose (**Chapter 6**); and the tandem increases of insulin resistance were less dramatic between NGT and prediabetes, increasing steadily across the spectrum of glycemia (**Chapters 5, 6**); (2) beta-cell function was a critical factor for those with early dysglycemia (iIFG and iIGT), above and beyond insulin resistance (**Chapter 5**); and (3) among individuals with prediabetes at baseline, both beta-cell function and insulin resistance were significantly associated with glycemia at one year (**Chapter 7**).

Taken together with data on beta-cell function in youth (85), this body of work provides cohesive evidence that declining beta-cell function occurs early in the pathogenesis of diabetes. Not only were marked differences in mean beta-cell function apparent between normoglycemia and mild dysglycemia (**Chapter 5**), but accelerated declines in beta-cell function were found even in normoglycemia (**Chapter 6**). **Chapters 5 and 7** showed that both beta-cell function and insulin resistance were important for

cross sectional and longer term levels of glycemia. Analyses utilized standardization as a technique to compare the relative importance of beta-cell function to insulin resistance and other factors associated with glycemia, and cross sectional analyses (**Chapter 5**) demonstrated that beta-cell function was significantly associated with glycemic status, more than any other variable, even insulin resistance. The relative significance of beta-cell function over insulin resistance was less apparent in longitudinal analyses (**Chapter 7**), however, this is likely due to the incomplete data set at the time of the dissertation analysis; new analyses which will include normoglycemic individuals (data expected in 2014) may clarify the longitudinal findings presented in this dissertation.

We present here one of the first studies to rigorously evaluate the relative contributions of beta-cell function (i.e., the oral disposition index) and insulin resistance in Asian Indian adults; other studies examining beta-cell function in Asian Indian adults are limited (123; 137-139) with beta-cell function not always evaluated rigorously according to the disposition index, a measure reflecting important, underlying biological constructs (i.e., beta-cell function is the amount of insulin secretion relative to the prevailing levels of insulin sensitivity in individuals) (35). These studies have produced conflicting findings, in which beta-cell function was associated with IGT (123), was not associated with IGT (137; 138), or appeared more associated with IFG than IGT (64; 139; 140). Nevertheless, one longitudinal study in Asian Indian adults which did not explicitly define beta-cell function using the disposition index showed that higher levels of the insulinogenic index (IGI) combined with improved insulin sensitivity were associated with the reversal of high-risk individuals from IGT to normoglycemia over 3

years (64). This study suggests that good beta-cell function is needed to maintain or possibly regain normoglycemia.

Drawing upon studies that have examined beta-cell function in other ethnicities, poor beta-cell function in early stages of the pathogenesis of diabetes is emerging as a critical factor in long term development of dysglycemia (41; 63; 87; 89). Individuals who eventually developed hyperglycemia first exhibited lower levels of beta-cell function (i.e. DI_o) years prior to the development of hyperglycemia (89; 119; 120). Moreover, the changes in beta-cell function appear to be greater compared to corresponding changes in insulin sensitivity at these early stages. In a cross sectional analysis of the Actos Now for Prevention of Diabetes study, when NGT participants with 2 –hour plasma glucose <5.55 mmol/L were defined as 100% normal, both insulin secretion and insulin sensitivity declined progressively across the spectrum of 2-hour glucose, however, the decline in insulin secretion was two- to threefold greater than the decline in insulin sensitivity (104). Our findings suggest that the association of beta-cell function is more significantly associated with dysglycemia (i.e., defined categorically as iIFG, iIGT, both IFG+IGT, or DM; and defined continuously as 2-hour glucose) than with insulin resistance, providing cross sectional and even longitudinal evidence of the important role of beta-cell function above and beyond insulin resistance in early stages of diabetes.

In the present study, while poor beta-cell function was comparable in individuals with iIFG and iIGT, patterns of decreasing beta-cell function across fasting glucose and 2-hour glucose differed (e.g., as shown in **Chapters 5 and 6**). The category, IFG, was first introduced by the American Diabetes Association in 1997 as a high risk state for type 2 diabetes and was originally meant to be analogous to the high-risk state of

impaired glucose tolerance, yet a variety of studies have shown that both categories represent unique segments of a population (89; 132; 141; 142). Discordance in these two high-risk states may be common because IFG is generally characterized as a state of raised hepatic glucose output and a defect in early insulin secretion, whereas IGT is characterized as a state of peripheral insulin resistance (121; 143). The impairment in early phase insulin secretion may be associated with both IFG and IGT, whereas impaired late phase insulin secretion may be associated with IGT only (132; 141). As stated earlier, studies have reported conflicting results in the metabolic abnormalities present in IFG and in IGT among Asian Indians and other ethnic groups, suggesting that our understanding of these two states or how they vary across populations is still limited.

Our findings showed that, while baseline beta-cell function was associated with fasting glucose, two-hour glucose, and HbA1c at one year follow-up (i.e., **Chapter 7**), the relative significance of beta-cell function to insulin resistance varied, with beta-cell function appearing to have the greatest relative association (i.e., compared to insulin resistance) with 2-hour glucose. These results may appear surprising, as IFG has been considered as a state of raised hepatic glucose output and a defect in early insulin secretion (121). The Inter99 study found that baseline insulin secretion (DI_o) was significantly impaired in normoglycemic individuals who subsequently progressed to isolated IFG, but during the development of isolated IFG, DI_o did not decrease further (89), and the authors suggest that progressive loss of beta-cell function occurred substantially in earlier stages of fasting glucose (i.e., during normoglycemia) and, subsequently, less dramatically in later stages of fasting glucose (i.e., during fasting hyperglycemia). Thus, in the present study, it is possible that the relative contributions

of insulin resistance appeared as great or greater than beta-cell function on estimated one-year levels of fasting glucose and HbA1c because our sample consisted only of individuals with prediabetes. If this is true, then future analyses of this cohort (which will include NGTs for longitudinal analyses) may show that DI_o plays an important role in fasting hyperglycemia and HbA1c, above and beyond insulin resistance. These possibilities are supported by a study of Japanese individuals, in which high normal HbA1c levels of 36-40 mmol/mol (5.4-5.8%) were associated with impaired insulin secretion without marked insulin resistance in Japanese individuals (122).

For all analyses, DI_o was selected as the primary measure of beta-cell function for several reasons, as also discussed in Chapter 5 (13). DI_o agrees with the biological constructs (e.g., the hyperbolic relationship of insulin secretion and sensitivity) known of beta cell function (35), as confirmed mathematically in this dissertation (**Chapter 5**) and in other more rigorously designed studies (41; 144). Longitudinal studies have indicated that DI_o is a good measure of disease processes related to beta cell function, as it predicts the development of future diabetes (41). The choice of 1/fasting insulin as the component of insulin sensitivity within DI_o is justified as well. The inverse of fasting insulin represents hepatic insulin sensitivity (i.e., rather than whole body insulin sensitivity), and for populations similar to the Asian Indian phenotype of central insulin resistance (e.g., lean with larger proportions of abdominal fat; younger levels of disease development), 1/fasting insulin may a particularly appropriate choice as a measure of insulin sensitivity compared to other measures (e.g., HOMA-S). Nevertheless, in the present dissertation, secondary measures of beta-cell function were calculated (**Chapter 5**), including $(\Delta I_{0\text{-}30} / \Delta G_{0\text{-}30})$ x (1/HOMA-IR); $(\Delta I_{0\text{-}30} / \Delta G_{0\text{-}30})$ x (modified Matsuda

Index); $AUC_{ins/glu}$ x (1/fasting insulin); and $AUC_{ins/glu}$ x (1/HOMA-IR); $AUC_{ins/glu}$ x (modified Matsuda Index). The hyperbolic curves detected between insulin secretion measures and 1/fasting insulin, and between insulin secretion and the modified Matsuda Index suggested that either 1/fasting insulin or the modified Matsuda Index are good measures to use in the calculation of DI_o. Regardless of the measure for insulin sensitivity used for its calculation, beta-cell function was consistently different between glycemic status groups (except between iIFG and iIGT), with NGT having the greatest beta cell function. Also, the percent difference in beta cell function comparing NGT to iIFG or to iIGT was greater when using other measures of insulin sensitivity to calculate beta cell function compared to using 1/fasting insulin (i.e., findings were the same as reported in the manuscript and slightly more pronounced). The use of the Matsuda Index within DI_o led to more extreme odds ratios of glycemic categories (unpublished analyses). These more extreme results suggest that the primary measure of DI_o in this dissertation (i.e., IGI x 1/fasting insulin) was a conservative, more cautious approach for the measurement of beta-cell function.

Findings of a hyperbolic relationship using DI_o are unlikely to be driven by autocollinearity, as detailed by Retnakaran and colleagues (145), for several, key reasons. First, the formulas used for each component of DI_o are not reciprocals (in which case one would expect hyperbolic relationship). Second, as shown in **Chapter 5**, the product resulting in DI_o are distinct for different degrees of glucose tolerance (whereas the product would have been the same across categories if they were reciprocals). Third, the product of insulin secretion and insulin sensitivity measured on separate days in the same individual still maintain a hyperbolic association, despite being derived from distinct measurements (145). While DI_o is an OGTT-derived measure, one not obtained from gold-standard intravenous techniques (see more discussion in limitations below) and one

that has not been validated specifically in Asian Indians, the reasons detailed above support the use of DI_o as a rigorous measure of beta-cell function.

Limitations

There are several limitations to this body of work. First, causality could not be ascertained, thus, our findings must be interpreted with caution; we cannot conclude that a decline in beta-cell function causes dysglycemia. Beta-cell decline can be caused by a variety of mechanisms, including inherent susceptibility, like genetic susceptibility, and through acquired mechanisms such as lipotoxicity, glucotoxicity, insulin resistance, deficiency in glucagon-like peptide-1, or gastric inhibitory polypeptide, making beta-cell dysfunction a secondary event (104). Furthermore, a decrease in beta-cell mass, due to amyloid deposits, may influence function (26). Despite this limitation of causality, we were able to show longitudinally that after one year of follow up, baseline levels of beta-cell function were highly associated with outcomes of glycemia.

Second, this study is limited by the degree of representation of the study sample. Results may not be generalizable to other populations. All study subjects were volunteers. Longitudinal analyses did not include subjects with NGT, but rather, all subjects had prediabetes at baseline. In addition, all subjects had a random blood glucose level of ≥ 6.1 mmol/L before receiving the OGTT. Thus, the NGT group may not be representative of normoglycemia. Moreover, subjects were also selected for overweight. Despite these limitations, our results, which indicate marked declines in beta-cell function across glycemia along with increases of insulin resistance, may be conservative results.

Third, we relied on OGTT-derived measures of beta-cell function rather than alternative methods (e.g., glucose clamp technique or frequently sampled intravenous glucose tolerance test, IVGTT) which originally showed that the relationship between insulin secretion and insulin sensitivity are hyperbolic in nature (i.e., y=constant/x) (35). However, the findings in this body of work are consistent with several other studies that relied on clamps and IVGTTs showing that poor insulin secretion begins during normoglycemia (63; 131) and occurs in iIFG and in iIGT (39; 119; 132). Also, OGTT-derived measures have been shown to be valid (41), consistent with biological constructs of the hyperbolic relationship between insulin secretion and insulin sensitivity (13; 144), and highly predictive of 10-year incidence of type 2 diabetes (41). Concurrently, OGTT-derived measures may harbor unique advantages for the study of diabetes pathogenesis, including the simulation of realistic metabolic responses after glucose ingestion that may play important roles in glucose metabolism (e.g., gluose disposition, incretin response, etc.). The current study used OGTTs to measure insulin secretion during glucose administration through the normal route, i.e., via the gastrointestinal tract, and these findings may be particularly useful for translational evidence. Another advantage of OGTT-based measures includes the ease of measuring beta-cell function in the context of a large, population-based setting compared to more laborious and invasive intravenous procedures. While error variance is large around DI_o, with variation in DI_o affected by within-subject variability, large samples enable correction for this variation and large sample sizes are sizes are generally more feasible in epidemiological studies (41; 145; 146). A minimum of 181 people were needed to detect a 20% change in the IGI, a number far exceeded in the present study.

Fourth, we were unable to measure complex physiological parameters that may impact blood glucose and insulin levels. For example, we did not measure glucosensitivity, rate sensitivity, or potentiation to measure beta cell function. Using modeling techniques, Gastaldelli and colleagues found that these dynamic parameters of beta-cell function and insulin sensitivity were independent determinants of 2-hour plasma glucose, and that they explained 89% of the variability of 2-hour plasma glucose levels (147; 148). Still, Gastaldelli's conclusions parallel the findings here; progressive decline in beta-cell function begins in "normal" glucose tolerant individuals. We also did not measure hepatic glucose release across subjects during fasting or OGTT and other physiological complexities excluded from the measure (147), thus we cannot consider hepatic extraction of newly secreted insulin or peripheral insulin elimination (95; 149). Nevertheless, we considered several different alternatives to the calculation of DI_o in Chapter 5, and we describe which alternative measures best met requirements for a hyperbolic relationship between insulin secretion and insulin sensitivity.

Strengths

This work contains several valuable strengths. First, 20,000 people from Chennai were screened in this large, community-based sample. All cases of diabetes were newly diagnosed. We focused on early stages of beta-cell function decline (prediabetes and normoglycemia), and complete analyses anticipated for early 2014 will include longitudinal analyses of normoglycemia individuals at baseline. We used a valid and rigorous measure of beta-cell function which meets well-accepted biological constructs (13), in which a hyperbolic relationship was found between insulin secretion and insulin

sensitivity (i.e., between IGI and 1/fasting insulin; IGI and the Matsuda Index; $AUC_{ins/glu}$ and 1/fasting insulin; and $AUC_{ins/glu}$ and Matsuda Index). Our study likely contains conservative estimates of decreased beta-cell function; if this study would have used a random sample, a greater proportion of the study sample would have consisted of NGTs, and even more dramatic differences in beta cell function would have been expected between NGT and prediabetes groups. All OGTTs were performed in the morning, which controlled for diurnal patterns of insulin secretion and insulin action (150). The results from this study have been demonstrated in Mexican American, Japanese, and other ethnicities (103), suggesting the findings from the present study are not only well-supported, but highlight important processes in diabetes development that bear relevance to a variety of populations.

Implications and Future Research

One of the practical implications of this study is that some populations may have an underlying, more stationary problem with beta-cell function. For example, if the findings in this body of work are replicated in a representative sample of Asian Indians, questions may then be directed to the susceptibility of Asian Indians to poor beta-cell function. DI_o has approximately 70% heritability, suggesting it has potential to be a useful trait for identifying genetic predisposition to type 2 diabetes (151). Multi-ethnic studies employing DI_o may help improve understanding of who is susceptible to poor beta-cell function. Future studies should consider this topic using a variety of measures for beta-cell function. In the present dissertation, we considered alternative OGTT derived measured, including $[(\Delta I_{0-30} / \Delta G_{0-30}) \times (1/\text{HOMA-IR})]$; $[(\Delta I_{0-30} / \Delta G_{0-30}) \times$ (modified Matsuda Index)]; $AUC_{ins/glu} \times (1/\text{fasting insulin})$; and $AUC_{ins/glu} \times (1/\text{HOMA-}$

IR); $AUC_{ins/glu}$ x (modified Matsuda Index). Our findings suggest that $AUC_{ins/glu}$ x (1/fasting insulin) and $AUC_{ins/glu}$ x (modified Matsuda Index) should be explored further as potentially useful OGTT-derived measures of beta-cell function.

In this analysis, while we studied DIo and insulin resistance in a community-based cohort, this body of work was not designed to predict risk of diabetes at any given glycemic point. Although our study suggests a threshold for fasting glucose, the cut-off may or may not be clinically useful for the purpose of identifying high-risk individuals for targeted prevention interventions. These findings could be used to start communication of a gradient risk as has been suggested as an alternative to defining a pre-diabetes state (152). Other studies have created prediction models of beta-cell decay in two phases, in which a long slow gradual loss of beta-cell function leads to a crisis in metabolic regulation, "precipitating a much more rapid decay phase" (153). Yet, in individuals with beta-cell function impairment, a late phase may or may not be present depending on the form of dysglycemia (fasting versus postchallenge) and prediction models based on oral tolerance have been limited (i.e., more have been based on *in vitro* models). One issue of prediction models is the selection of a glycemia measure. OGTTs may provide a better tool to identify subjects with beta-cell function failure compared with HbA1c. This conclusion is based on the observation that when subjects were stratified on the basis of OGTT results, those with IFG and or IGT (despite having HbA1c <5.7%) had marked decreases in beta-cell function compared with subjects with NGT (55% decrease in DIo) (105). Challenging the beta-cell with a glucose load may provide a "stress test" to the beta-cell and expose more subtle decreases in beta-cell function compared with mesurements taken during the fasting state. Assessment of beta-

cell health using an OGTT may be particularly important for identification of future risk of type 2 diabetes (105). Thus, with additional longitudinal and multi-ethnic studies, this body of work may lead to the creation of prediction models for prediabetes.

In addition to the aforementioned, this body of work may lead to additional research in insulin secretion characterization and reversion from prediabetes to normoglycemia. We did not explore specific OGTT insulin concentration patterns, which has recently been found in a longitudinal study to predict subsequent development of type 2 diabetes, independent of insulin secretion, insulin sensitivity, age, sex, family history, and BMI at baseline (40). Also, as we receive follow up data from normoglycemic individuals at baseline, we will be able to better characterize 'reversion' from prediabetes to normoglycemia. This has been documented in lifestyle intervention trials, with a range including 19% in controls in the DPP to 80% of participants with IFG have 10 years of follow up (22). This phenomenon has been measured before (22), however, pathophysiological measures (e.g., beta-cell function) were not considered. Creating new phenotypes based on beta-cell function along with insulin resistance may help identify non-hyperglycemic stages of diabetes and prediabetes that can better reflect pathophysiology of the disease, which may include individuals who are currently classified as normoglycemic (154; 155).

The significant beta-cell dysfunction at the time of diagnosis that is seen in adults appears to be comparable to adolescents with newly diagnosed type 2 diabetes (156). A recent study in Asian Indian youth also emphasized the importance of beta-cell dysfunction relative to insulin resistance in hyperglycemia (85). Furthermore, studies from other ethnicities are highlighting the impairment of insulin secretion, relative to

insulin resistance, in the development of diabetes in youth (157-159). These findings highlight the potential to identify new strategies for research in diabetes prevention and control that incorporate beta cell function preservation for adults as well as youth. While it is important to recognize that any intervention targeting one physiological risk factor alone cannot be the sole solution to diabetes across large, diverse population settings (160), new approaches to prevent beta-cell dysfunction may offer new, far-reaching impact across ages and ethnic groups. Future research will need to determine new diabetes prevention strategies and treatments that can target the preservation of beta-cell function and determine whether these interventions can target both youth and adults in a cost-effective manner.

Conclusions

Data from this large, community-based study of Asian Indians suggest that reduced beta-cell function is prominent at glycemic levels that are clinically defined as normoglycemia. Furthermore, reduced beta-cell function may play a greater role in the development of prediabetes than insulin resistance. Validation in representative, multi-ethnic cohorts is needed to corroborate these findings, which suggest that early preservation of beta-cell function may be important in seemingly healthy individuals. Future lifestyle intervention studies should test the effects of improved diet, increased physical activity, and reduced weight on the beta-cell function of individuals and not just their insulin resistance.

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